WEST Search History

DATE: Monday, May 13, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR			
L18	L1 and (platelet$4 near activation)	3	L18
L17	L16 and vegf	53	L17
L16	L15 and activation	53	L16
L15	L11 and vegf$8 and platelet$4	54	L15
DB=USPT; PLUR=YES; OP=OR			
L14	4456550.pn.	1	L14
L13	(6261535)[PN] OR (5965132)[PN]	2	L13
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR			
L12	L11 and vegf$8	54	L12
L11	L10 and administ$8	115	L11
L10	L9 and (vwf or willebrand)	121	L10
L9	L8 and bifunctional	1121	L9
L8	thromb$6	43798	L8
L7	L6 and willebrand	5	L7
L6	(stewart)[IN] OR (person)[IN] or(noujaim)[in]	13554	L6
L5	(stewart)[IN] OR (person)[IN]	13459	L5
L4	L3 and wilms	1	L4
L3	hla-A2.1 or hla-a0201	135	L3
L2	L1 and wilms	10	L2
L1	(stauss)[IN] OR (gao)[IN]	3542	L1

END OF SEARCH HISTORY

(FILE 'HOME' ENTERED AT 10:43:02 ON 13 MAY 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 10:43:14 ON 13 MAY 2002

L1	704921	S THROMB?
L2	12366	S L1 AND WILLEBRAND
L3	0	S L2 AND BIFINCTION?
L4	8	S L2 AND BIFUNCTION?
L5	5	DUP REM L4 (3 DUPLICATES REMOVED)
L6	49	S L2 AND VEGF?
L7	24	DUP REM L6 (25 DUPLICATES REMOVED)
L8	0	S L7 AND ADMINIST?
L9	6154	S STEWART M?/AU OR PERSON R?/AU OR NOUJAIM A?/AU
L10	60	S L9 AND (VWF OR WILLEBRAND?)
L11	28	DUP REM L10 (32 DUPLICATES REMOVED)
L12	38450	S L1 AND (CANCER? OR NEOPLAST? OR ANGIO? TUMOR? OR TUMOUR?)
L13	258	S L12 AND (VWF OR WILLEBRAND)
L14	14	S L13 AND VEGF?
L15	6	DUP REM L14 IBIB ABS (8 DUPLICATES REMOVED)

Gabby O'Cailla

2nct

1888-
999-
1093
ext 310

09/738970

09/207277 (6261535) 9-17-01
↳ 1218198

08/350212 (5965132) 12-5-94
← 6/2/94

61 54321

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FILE 'HOME' ENTERED AT 10:43:02 ON 13 MAY 2002

=> file medline caplus embase biosis
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'MEDLINE' ENTERED AT 10:43:14 ON 13 MAY 2002

FILE 'CAPLUS' ENTERED AT 10:43:14 ON 13 MAY 2002
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FILE 'BIOSIS' ENTERED AT 10:43:14 ON 13 MAY 2002
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=> s thromb?
L1      704921 THROMB?

=> s l1 and willebrand
L2       12366 L1 AND WILLEBRAND

=> s l2 and bifinction?
L3           0 L2 AND BIFINCTION?

=> s l2 and bifunction?
L4           8 L2 AND BIFUNCTION?

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5           5 DUP REM L4 (3 DUPLICATES REMOVED)

=> dis l5 1-5 ibib abs kwic

L5   ANSWER 1 OF 5  EMBASE  COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER:   95141904  EMBASE
DOCUMENT NUMBER:    1995141904
TITLE:              Interaction of the von Willebrand factor (vWF)
                    with collagen. Localization of the primary collagen-binding
                    site by analysis of recombinant vWF a domain polypeptides.
AUTHOR:             Cruz M.A.; Yuan H.; Lee J.R.; Wise R.J.; Handin R.I.
CORPORATE SOURCE:   Hematology-Oncology Div., Brigham and Women's Hospital, 75
                    Francis St.,Boston, MA 02115, United States
SOURCE:             Journal of Biological Chemistry, (1995) 270/18
                    (10822-10827).
                    ISSN: 0021-9258  CODEN: JBCHA3
COUNTRY:            United States
DOCUMENT TYPE:      Journal; Article
FILE SEGMENT:       025     Hematology
                    029     Clinical Biochemistry
LANGUAGE:           English
SUMMARY LANGUAGE:   English
AB   The von Willebrand factor (vWF) mediates platelet adhesion to
     the vascular subendothelium by binding to collagen, other matrix
     constituents, and the platelet receptor glycoproteins Ib/IX and IIb/IIIa.
     Although substantial progress has been made in defining vWF
     structure-function relationships, there are conflicting data regarding the
     location of its collagen-binding site(s). Possible collagen-binding sites
     have been localized in the A1 and A3 domains of vWF. To study the proposed
     binding sites, we have expressed cDNA sequences encoding the A1 and A3
     domains of vWF in Escherichia coli and purified the resulting proteins
     from bacterial inclusion bodies. In addition, a chimeric molecule
     containing residues 465-598 of the vWF A1 domain polypeptide (vWF-A1)
     fused in frame to residues 1018-1114 of the vWF A3 domain polypeptide
     (vWF-A3) was also expressed. Each of the three recombinant proteins
     purified as a monomer and contained a single disulfide bond. As previously
     reported (Cruz, M. A. Handin, R. I., and Wise, R. J. (1993) J. Biol. Chem.
     268, 21238-21245), recombinant vWF-A1 inhibited ristocetin- induced
     platelet agglutination, but did not compete with vWF multimers for
     collagen binding. In contrast, vWF-A3 inhibited the binding of multimeric
     vWF to immobilized collagen, but did not inhibit ristocetin-induced
     platelet agglutination. Metabolically labeled vWF-A3 bound to immobilized
     collagen in a saturable and reversible manner with a K(d) of 1.8 x 10-6 M.
     The vWF- A1/A3 chimera was bifunctional. It inhibited vWF
     binding to platelet glycoprotein Ib/IX with an IC50 of 0.6 x 10-6 M and
     inhibited vWF binding to collagen with an IC50 of 0.5-1.0 x 10-6 M. These
     results, taken together, provide firm evidence that the major
     collagen-binding site in vWF resides in the A3 domain.
TI   Interaction of the von Willebrand factor (vWF) with collagen.
     Localization of the primary collagen-binding site by analysis of
     recombinant vWF a domain polypeptides.
AB   The von Willebrand factor (vWF) mediates platelet adhesion to
     the vascular subendothelium by binding to collagen, other matrix
     constituents, and the platelet receptor.  .  .  collagen in a saturable
     and reversible manner with a K(d) of 1.8 x 10-6 M. The vWF- A1/A3 chimera
     was bifunctional. It inhibited vWF binding to platelet
     glycoprotein Ib/IX with an IC50 of 0.6 x 10-6 M and inhibited vWF binding.
     .  .
CT   Medical Descriptors:
     *binding site
       *thrombocyte
     animal cell
     article
     controlled study
     disulfide bond
     dna sequence
     escherichia coli
     fast protein liquid chromatography
     nonhuman
     polyacrylamide gel electrophoresis
     priority journal
     structure activity relation
     subendothelium
       thrombocyte adhesion
       thrombocyte agglutination
```

*collagen type 1
*glycoprotein ib
*glycoprotein iib
*glycoprotein iiia
*von willebrand factor
complementary dna
disulfide
polypeptide
recombinant protein
recombinant von willebrand factor
ristocetin
unclassified drug

RN (von willebrand factor) 109319-16-6; (disulfide) 16734-12-6; (ristocetin) 11006-74-9, 11140-99-1, 1404-55-3

L5 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:45956 CAPLUS
DOCUMENT NUMBER: 120:45956
TITLE: Bifunctional antithrombotic molecules and antithrombotic polypeptides
INVENTOR(S): Ruggeri, Zaverio M.; Ware, Jerry L.; De Marco, Luigi; Mazzucato, Mario
PATENT ASSIGNEE(S): Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9311778	A1	19930624	WO 1992-US10947	19921211
W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
AU 9333266	A1	19930719	AU 1993-33266	19921211

PRIORITY APPLN. INFO.: US 1991-806709 19911212
WO 1992-US10947 19921211

AB Proteins or their org. analogs capable of inhibiting the binding of **thrombins** and von **Willebrand** factor to platelet glycoprotein Ib.alpha. (GPIb.alpha.) are provided for use as inhibitors of platelet activation and aggregation at damaged or diseased vascular sites. The **bifunctional** mol. comprises (1) an analog of the GPIb.alpha. binding site for **thrombin** and (2) an analog of the GPIb.alpha. binding site for von **Willebrand** factor or a von **Willebrand** factor fragment contg. all or part of its binding site for GPIb.alpha.. Smaller peptides derived from these proteins may also be used as antithrombotics, e.g. peptides contg. sulfated tyrosine (no data). Synthetic peptide analogs of the **thrombin**-binding domains of GPIb.alpha. were prepd. and shown to be capable of inhibiting platelet binding of **thrombin**. The construction of expression vectors for manuf. of large peptides derived from GPIb.alpha. and low-cysteine analogs of von **Willebrand** factor in animal cell systems are demonstrated.

TI **Bifunctional** antithrombotic molecules and antithrombotic polypeptides

AB Proteins or their org. analogs capable of inhibiting the binding of **thrombins** and von **Willebrand** factor to platelet glycoprotein Ib.alpha. (GPIb.alpha.) are provided for use as inhibitors of platelet activation and aggregation at damaged or diseased vascular sites. The **bifunctional** mol. comprises (1) an analog of the GPIb.alpha. binding site for **thrombin** and (2) an analog of the GPIb.alpha. binding site for von **Willebrand** factor or a von **Willebrand** factor fragment contg. all or part of its binding site for GPIb.alpha.. Smaller peptides derived from these proteins may also be used as antithrombotics, e.g. peptides contg. sulfated tyrosine (no data). Synthetic peptide analogs of the **thrombin**-binding domains of GPIb.alpha. were prepd. and shown to be capable of inhibiting platelet binding of **thrombin**. The construction of expression vectors for manuf. of large peptides derived from GPIb.alpha. and low-cysteine analogs of von **Willebrand** factor in animal cell systems are demonstrated.

ST platelet inhibitor glycoprotein GPIbalpha analog; von **Willebrand** factor analog platelet inhibitor

IT Antibodies
RL: BIOL (Biological study)
(anti-**thrombin** or von **Willebrand** factor, in **bifunctional** platelet aggregation inhibitors)

IT Protein sequences
(of platelet aggregation-inhibiting peptides derived from glycoprotein GPIb.alpha. and von **Willebrand** factor)

IT Anticoagulants and Antithrombotics
Blood platelet aggregation inhibitors
(peptides contg. glycoprotein GPIb.alpha. binding sites for **thrombin** and von **Willebrand** factor as)

IT Glycolipoproteins
RL: SPN (Synthetic preparation); PREP (Preparation)
(GPIb, .alpha. subunit, **thrombin** and von **Willebrand** factor binding to, prepn. of inhibitors for)

IT Blood vessel, composition
(endothelium, **thrombin** and von **Willebrand** factor binding sites of cells of, peptides contg. glycoprotein GPIb.alpha. as)

IT Antibodies
RL: BIOL (Biological study)
(monoclonal, LJ-Ib10 and LJ-Ib1, anti-**thrombin** and von **Willebrand** factor, in **bifunctional** platelet aggregation inhibitors)

IT Muscle
(smooth, **thrombin** and von **Willebrand** factor binding to cells of, peptides contg. glycoprotein GPIb.alpha. binding sites for **thrombin** and von **Willebrand** factor as inhibitors for)

IT Peptides, uses
RL: USES (Uses)
(sulfotyrosine-contg., as platelet **thrombin**-binding inhibitor, from glycoprotein GPIb.alpha., **bifunctional** fusion proteins in relation to)

IT 143750-77-0, Methionyl [475-733] von **Willebrand** factor (human)
143750-78-1, Methionyl [492-733] von **Willebrand** factor (human)
143750-79-2, Methionyl [508-733] von **Willebrand** factor (human)
151087-75-1, [441-709] Von **Willebrand** factor (human)

151087-76-2, [441-704] Von **Willebrand** factor (human)
151087-77-3, [441-700] Von **Willebrand** factor (human)
151087-78-4, [441-696] Von **Willebrand** factor (human)
RL: PRP (Properties)
(amino acid sequence of, as platelet aggregation and activation inhibitor, glycoprotein GPIb.alpha. binding in relation to)

IT 125890-03-1, [271-285] Gycoprotein GPIb.alpha. (human) 151681-37-7
151841-58-6, [269-282] Glycoprotein GPIb.alpha. (human)
RL: PRP (Properties)
(amino acid sequence of, platelet aggregation and activation inhibitor, inhibition of glycoprotein GPIb.alpha. binding to **thrombin** by)

IT 152084-81-6
RL: PRP (Properties)
(amino acid sequence of, platelet aggregation and activation inhibitor, **thrombin**-binding peptide in relation to)

IT 126124-79-6, [1-293] Glycoprotein GPIb.alpha. (human)
RL: PRP (Properties)
(amino acid sequence of, platelet aggregation and activation inhibitors derived from, **thrombin**-binding peptide in relation to)

IT 109319-16-6D, low cysteine analogs, fusion products with glycoprotein Ib.alpha. **thrombin** binding site
RL: BIOL (Biological study)
(as platelet aggregation and activation inhibitors)

IT 109319-16-6
RL: BIOL (Biological study)
(glycoprotein GPIb.alpha. binding to **thrombin** and, prepn. of inhibitors for)

IT 9002-04-4, **Thrombin**
RL: BIOL (Biological study)
(glycoprotein Ib.alpha. peptides binding to von **Willebrand**'s factor and, prepn. of inhibitors for)

IT 137750-42-6P, [1-302] Glycoprotein GPIb.alpha. (human)
RL: PREP (Preparation)
(manuf. in animal cells of, platelet aggregation and activation inhibitor peptides derived from, inhibition of **thrombin** binding in relation to)

L5 ANSWER 3 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93106271 EMBASE
DOCUMENT NUMBER: 1993106271
TITLE: Synthetic peptides inhibit the interaction of von **Willebrand** factor-platelet membrane glycoproteins.
AUTHOR: Mohri H.; Zimmerman T.S.; Ruggeri Z.M.
CORPORATE SOURCE: First Dept. of International Med., Yokohama City Univ. School of Med., 3-9 Fukuura,Kanazawa-ku, Yokohama 236, Japan
SOURCE: Peptides, (1993) 14/2 (125-129).
ISSN: 0196-9781 CODEN: PEPTDO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
025 Hematology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We synthesized peptides of the general formula Argn, Lysn, and (Lys-Arg)n. These agents inhibited the ristocetin-mediated binding of vWF to GPIb and the binding of asialo-vWF to platelets. This inhibitory activity was proportional to the number of lysine and/or arginine residues/molecules present. Peptides to which the sequence of Arg-Gly-Asp-Val (RGDV) had been added at the carboxy-terminus of (Lys-Arg)n, Lysn, or Argn also inhibited vWF binding. Peptides with an RGDV sequence were found to block the binding of 125I-fibrinogen to ADP-stimulated platelets. These findings indicate that the general formulae (Lys-Arg)n, Lysn, and Argn with an RGDV sequence inhibit the binding of fibrinogen to activated platelets as well as the binding of vWF to GPIb. Thus, these peptides may behave as **bifunctional** antiplatelet agents.

TI Synthetic peptides inhibit the interaction of von **Willebrand** factor-platelet membrane glycoproteins.

AB . . . of fibrinogen to activated platelets as well as the binding of vWF to GPIb. Thus, these peptides may behave as **bifunctional** antiplatelet agents.

CT Medical Descriptors:
*cell membrane
***thrombocyte aggregation**
article
controlled study
human
human cell
priority journal
*glycoprotein
*adenosine diphosphate
*amino acid
*arginine
*fibrinogen
*glycine
*ristocetin
*synthetic peptide: DV, drug development
***von willebrand factor**

RN. . . 58-64-0; (amino acid) 65072-01-7; (arginine) 1119-34-2, 15595-35-4, 7004-12-8, 74-79-3; (fibrinogen) 9001-32-5; (glycine) 56-40-6, 6000-43-7, 6000-44-8; (ristocetin) 11006-74-9, 11140-99-1, 1404-55-3; (von **willebrand** factor) 109319-16-6

L5 ANSWER 4 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 91242626 EMBASE
DOCUMENT NUMBER: 1991242626
TITLE: Dimeric ristocetin flocculates proteins, binds to platelets, and mediates von **Willebrand** factor-dependent agglutination of platelets.
AUTHOR: Scott J.P.; Montgomery R.R.; Retzinger G.S.
CORPORATE SOURCE: Dept. of Pediatrics, Medical Coll. of Wisconsin,Milwaukee, WI 53226, United States
SOURCE: Journal of Biological Chemistry, (1991) 266/13 (8149-8155).
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
029 Clinical Biochemistry
052 Toxicology

LANGUAGE: English
SUMMARY LANGUAGE: English

AB Ristocetin in aqueous solution dimerizes with an equilibrium dissociation constant of 5.0 x 10-4 M, i.e. .apprx.1.1 mg ml-1 (Waltho, J. P., and Williams, D. H. (1989) J. Am. Chem. Soc. 111, 2475-2480). At concentrations of about 1.0 mg ml-1 ristocetin flocculates many proteins, lyses platelets and, in the presence of von **Willebrand** factor, agglutinates both fresh and formalin-fixed platelets. Because ristocetin exists as both monomeric and dimeric species, we sought to determine which of these forms flocculates proteins and agglutinates platelets. We found that: 1) the initial rate of flocculation of certain proteins, 2) the initial rate of agglutination of formalin-fixed platelets, and 3) the binding of ristocetin to formalin-fixed platelets are higher order solely with respect to the concentration of ristocetin dimers. As to the operative mechanism, it appears that **bifunctional** dimers cross-link proteins that possess multiple copies of a common recognition site. Preliminary evidence indicates that a recognition site is a .beta.-turn of the form X-P-G-X'.

TI Dimeric ristocetin flocculates proteins, binds to platelets, and mediates von **Willebrand** factor-dependent agglutination of platelets.

AB . . . 2475-2480). At concentrations of about 1.0 mg ml-1 ristocetin flocculates many proteins, lyses platelets and, in the presence of von **Willebrand** factor, agglutinates both fresh and formalin-fixed platelets. Because ristocetin exists as both monomeric and dimeric species, we sought to determine. . . are higher order solely with respect to the concentration of ristocetin dimers. As to the operative mechanism, it appears that **bifunctional** dimers cross-link proteins that possess multiple copies of a common recognition site. Preliminary evidence indicates that a recognition site is. . .

CT Medical Descriptors:
***thrombocyte aggregation**
article
dimerization
priority journal
*ristocetin: PD, pharmacology
*ristocetin: AN, drug analysis
***von willebrand factor**

RN (ristocetin) 11006-74-9, 11140-99-1, 1404-55-3; (von **willebrand** factor) 109319-16-6

L5 ANSWER 5 OF 5 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 86112521 MEDLINE
DOCUMENT NUMBER: 86112521 PubMed ID: 3003157
TITLE: Identification of the **thrombin** receptor on human platelets by chemical crosslinking.
AUTHOR: Takamatsu J; Horne M K 3rd; Gralnick H R
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1986 Feb) 77 (2) 362-8. Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198603
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860326

AB To identify the molecular site of **thrombin** binding to the platelet membrane, we covalently linked 125I-**thrombin** to platelets by using the **bifunctional** chemical cross-linking agents disuccinimidyl suberate and dithiobis(succinimidyl propionate). The proteins cross-linked to 125I-**thrombin** by this method were analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and followed by autoradiography. Two radiolabeled **thrombin** complexes were identified, a major species of Mr approximately 200,000 and a minor one of Mr approximately 400,000. Hirudin prevented the formation of both complexes. The radioactivity of the approximately 200,000-Mr complex was always 7-10-fold greater than the radioactivity of the approximately 400,000-Mr complex regardless of the **thrombin** concentration to which the platelets were exposed (0.1-29 nM). Although 125I-**thrombin** complexes generated with **thrombasthenic** platelets (lacking glycoprotein IIb/IIIa) were indistinguishable from normal, no complexes appeared when Bernard-Soulier platelets (lacking glycoprotein Ib [GPIb]) were used. Complex formation was blocked by rabbit antiglycocalicin antiserum, but not by the monoclonal antibody 6D1, which is directed against the site on GPIb where von **Willebrand** factor (vWf) binds in the presence of ristocetin. Although cross-linking studies suggested that vWf might partially inhibit **thrombin** binding to platelets, this was not confirmed by equilibrium binding studies in the presence of vWf and ristocetin. The data suggest, therefore, that at all **thrombin** concentrations binding occurs at the same membrane site, despite evidence from equilibrium studies for high and low affinity classes of receptors, and that the approximately 400,000-Mr complex is simply a dimer of the approximately 200,000-Mr species. We conclude that the membrane site to which **thrombin** binds is the glycocalicin portion of platelet GPIb at a site remote from the point of ristocetin-dependent vWf binding.

TI Identification of the **thrombin** receptor on human platelets by chemical crosslinking.

AB To identify the molecular site of **thrombin** binding to the platelet membrane, we covalently linked 125I-**thrombin** to platelets by using the **bifunctional** chemical cross-linking agents disuccinimidyl suberate and dithiobis(succinimidyl propionate). The proteins cross-linked to 125I-**thrombin** by this method were analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and followed by autoradiography. Two radiolabeled **thrombin** complexes were identified, a major species of Mr approximately 200,000 and a minor one of Mr approximately 400,000. Hirudin prevented. . . of the approximately 200,000-Mr complex was always 7-10-fold greater than the radioactivity of the approximately 400,000-Mr complex regardless of the **thrombin** concentration to which the platelets were exposed (0.1-29 nM). Although 125I-**thrombin** complexes generated with **thrombasthenic** platelets (lacking glycoprotein IIb/IIIa) were indistinguishable from normal, no complexes appeared when Bernard-Soulier platelets (lacking glycoprotein Ib [GPIb]) were used.. . . rabbit antiglycocalicin antiserum, but not by the monoclonal antibody 6D1, which is directed against the site on GPIb where von **Willebrand** factor (vWf) binds in the presence of ristocetin. Although cross-linking studies suggested that vWf might partially inhibit **thrombin** binding to platelets, this was not confirmed by equilibrium binding studies in the presence of vWf and ristocetin. The data suggest, therefore, that at all **thrombin** concentrations binding occurs at the same membrane site,

despite evidence from equilibrium studies for high and low affinity classes of. . . approximately 400,000-Mr complex is simply a dimer of the approximately 200,000-Mr species. We conclude that the membrane site to which **thrombin** binds is the glycocalicin portion of platelet GPIb at a site remote from the point of ristocetin-dependent vWf binding.

CT . . .

Glycoproteins: BL, blood
Glycoproteins: IM, immunology
Hirudin: PD, pharmacology
Immune Sera: PD, pharmacology
Molecular Weight
*Receptors, Cell Surface: ME, metabolism
Receptors, Thrombin
Succinimides
Thrombin: ME, metabolism

CN 0 (Cross-Linking Reagents); 0 (Glycoproteins); 0 (Immune Sera); 0 (Receptors, Cell Surface); 0 (Receptors, **Thrombin**); 0 (Succinimides); EC 3.4.21.5 (**Thrombin**)

=> dis his

(FILE 'HOME' ENTERED AT 10:43:02 ON 13 MAY 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 10:43:14 ON 13 MAY 2002
L1 704921 S THROMB?
L2 12366 S L1 AND WILLEBRAND
L3 0 S L2 AND BIFINCTION?
L4 8 S L2 AND BIFUNCTION?
L5 5 DUP REM L4 (3 DUPLICATES REMOVED)

=> s l2 and VEGF?
L6 49 L2 AND VEGF?

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7 24 DUP REM L6 (25 DUPLICATES REMOVED)

=> sl7 and administ?
SL7 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l7 and administ?
L8 0 L7 AND ADMINIST?

=> dis l6 ibib abs

L6 ANSWER 1 OF 49 MEDLINE
ACCESSION NUMBER: 2002182450 IN-PROCESS
DOCUMENT NUMBER: 21913062 PubMed ID: 11916242
TITLE: Aerosol delivery of PEI-p53 complexes inhibits B16-F10 lung metastases through regulation of angiogenesis.
AUTHOR: Gautam Ajay; Densmore Charles L; Melton Sara; Golunski Eva; Waldrep J Clifford
CORPORATE SOURCE: Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, Texas 77030, USA.
SOURCE: CANCER GENE THERAPY, (2002 Jan) 9 (1) 28-36. Journal code: 9432230. ISSN: 0929-1903.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020403
Last Updated on STN: 20020403

AB Inhibition of pulmonary metastases poses a difficult clinical challenge for current therapeutic regimens. We have developed an aerosol system utilizing a cationic polymer, polyethyleneimine (PEI), for topical gene delivery to the lungs as a novel approach for treatment of lung cancer. Using a B16-F10 murine melanoma model in C57BL/6 mice, we previously demonstrated that aerosol delivery of PEI-p53 DNA resulted in highly significant reductions in the tumor burden ($P < .001$) in treated animals, and also lead to about 50% increase in the mean length of survival of the mice-bearing B16-F10 lung tumors. The mechanisms of this antitumor effect of p53 are investigated in this report. Here, we demonstrate that the p53 transfection leads to an up-regulation of the antiangiogenic factor **thrombospondin**-1 (TSP-1) in the lung tissue and the serum of the mice. Furthermore, there is a down-regulation of vascular endothelial growth factor (**VEGF**) in the lung tissue and serum of the B16-F10 tumor-bearing mice treated with PEI-p53 DNA complexes, compared with untreated tumor-bearing animals. In addition, staining for von **Willebrand** factor (vWF), a marker for the angiogenic blood vessels, revealed that p53 treatment leads to a decrease in the angiogenic phenotype of the B16-F10 tumors. Immunohistochemistry for transgene expression reveals that the PEI-p53 aerosol complexes transfect mainly the epithelial cells lining the airways, with diffuse transfection in the alveolar lining cells, as well as, the tumor foci in the lung tissue. There was also some evidence of apoptosis in the lung tumor foci of animals treated with p53. The data suggest that aerosol delivery of PEI-p53 complexes leads to inhibition of B16-F10 lung metastases, in part by suppression of angiogenesis.

=> dis l6 ibib abs 2-49

L6 ANSWER 2 OF 49 MEDLINE
ACCESSION NUMBER: 2002164482 MEDLINE
DOCUMENT NUMBER: 21893577 PubMed ID: 11896208
TITLE: Analysis of intrapulmonary vessels and epithelial-endothelial interactions in the human developing lung.
AUTHOR: Maeda Sumiko; Suzuki Satoshi; Suzuki Takashi; Endo Mareyuki; Moriya Takuya; Chida Masayuki; Kondo Takashi; Sasano Hironobu
CORPORATE SOURCE: Department of Thoracic Surgery, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan.. sumiko@idac.tohoku.ac.jp
SOURCE: LABORATORY INVESTIGATION, (2002 Mar) 82 (3) 293-301. Journal code: 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020317
Last Updated on STN: 20020405
Entered Medline: 20020404

AB The establishment of a sufficiently wide and functional blood-gas interface is of critical importance in lung development, but development of the intrapulmonary vascular system including alveolar capillary vessels still remains unclear. In this study, we first characterized the structural development of the vascular system in accordance with that of airways in human fetal lungs at the pseudoglandular phase (8, 13, and 16 weeks gestation) by examining the immunohistochemical distribution of CD34 and alpha-smooth muscle actin (SMA). Using double immunohistochemistry and 3-dimensional reconstruction techniques, endothelial cells in the developing lung could be classified into two different types according to the characteristics of their adjacent cells (presence or absence of SMA-positive cells) and their distribution (proximal or distal lung parenchyme). Endothelial cells without SMA-positive cells developed into a capillary network surrounding the budding components of distal airways during the mid-pseudoglandular phase before communicating with proximal vessels. We then examined the immunoreactivity of **thrombomodulin** and von **Willebrand** factor (vWF) in endothelial cells. Endothelial cells of the capillary network were mainly positive for vWF during the early gestational stages, but altered their phenotypes to those of mature lungs (vWF negative and **thrombomodulin** positive) during the terminal sac phase. We subsequently determined the immunohistochemical distribution of vascular endothelial growth factor (**VEGF**). Epithelial cells of the most distal airways were intensely positive for **VEGF**. These results suggest that **VEGF** present in airway epithelial cells is involved in the maturation as well as proliferation of capillary endothelial cells. Epithelial-endothelial interactions during lung development are considered very important in the establishment of the functional blood-gas interface.

L6 ANSWER 3 OF 49 MEDLINE
ACCESSION NUMBER: 2002092030 MEDLINE
DOCUMENT NUMBER: 21676344 PubMed ID: 11744618
TITLE: Connective tissue growth factor binds vascular endothelial growth factor (**VEGF**) and inhibits **VEGF** -induced angiogenesis.
AUTHOR: Inoki Isao; Shiomi Takayuki; Hashimoto Gakuji; Enomoto Hiroyuki; Nakamura Hiroyuki; Makino Ken-ichi; Ikeda Eiji; Takata Shigeo; Kobayashi Ken-ichi; Okada Yasunori
CORPORATE SOURCE: Department of Pathology, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-0016, Japan.
SOURCE: FASEB JOURNAL, (2002 Feb) 16 (2) 219-21.
Journal code: 8804484. ISSN: 1530-6860.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020201
Last Updated on STN: 20020404
Entered Medline: 20020403

AB Vascular endothelial growth factor (**VEGF**) is a strong angiogenic mitogen and plays important roles in angiogenesis under various pathophysiological conditions. The in vivo angiogenic activity of secreted **VEGF** may be regulated by extracellular inhibitors, because it is also produced in avascular tissues such as the cartilage. To seek the binding inhibitors against **VEGF**, we screened the chondrocyte cDNA library by a yeast two-hybrid system by using **VEGF165** as bait and identified connective tissue growth factor (CTGF) as a candidate. The complex formation of **VEGF165** with CTGF was first established by immunoprecipitation from the cells overexpressing both binding partners. A competitive affinity-binding assay also demonstrated that CTGF binds specifically to **VEGF165** with two classes of binding sites (Kd = 26 +/- 11 nM and 125 +/- 38 nM). Binding assay using deletion mutants of CTGF indicated that the **thrombospondin** type-1 repeat (TSP-1) domain of CTGF binds to the exon 7-coded region of **VEGF165** and that the COOH-terminal domain preserves the affinity to both **VEGF165** and **VEGF121**. The interaction of **VEGF165** with CTGF inhibited the binding of **VEGF165** to the endothelial cells and the immobilized KDR/IgG Fc; that is, a recombinant protein for **VEGF165** receptor. By in vitro tube formation assay of endothelial cells, full-length CTGF and the deletion mutant possessing the TSP-1 domain inhibited **VEGF165**-induced angiogenesis significantly in the complex form. This antiangiogenic activity of CTGF was demonstrated further by in vivo angiogenesis assay by using Matrigel injection model in mice. These data demonstrate for the first time that **VEGF165** binds to CTGF through a protein-to-protein interaction and suggest that the angiogenic activity of **VEGF165** is regulated negatively by CTGF in the extracellular environment.

L6 ANSWER 4 OF 49 MEDLINE
ACCESSION NUMBER: 2001642260 MEDLINE
DOCUMENT NUMBER: 21553580 PubMed ID: 11696172
TITLE: Angiogenesis and phenotypic alteration of alveolar capillary endothelium in areas of neoplastic cell spread in primary lung adenocarcinoma.
AUTHOR: Jin E; Ghazizadeh M; Fujiwara M; Nagashima M; Shimizu H; Ohaki Y; Arai S; Gomibuchi M; Takemura T; Kawanami O
CORPORATE SOURCE: Department of Molecular Pathology, Institute of Gerontology, Nippon Medical School, Kawasaki, Japan.
SOURCE: PATHOLOGY INTERNATIONAL, (2001 Sep) 51 (9) 691-700.
Journal code: 9431380. ISSN: 1320-5463.
PUB. COUNTRY: Australia
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011107
Last Updated on STN: 20020123
Entered Medline: 20011214

AB Normal alveolar capillary endothelium is quiescent in nature and displays anticoagulant **thrombomodulin** (TM) on its surface. The cytoplasms of these endothelial cells are ultrastructurally non-fenestrated type, and they barely express von **Willebrand** factor (vWf). Alveolar fibrosis is accompanied by a capillary endothelium reactive for vWf, and a loss of TM expression. In primary lung adenocarcinoma, neovascularization occurs in association with alveolar fibrosis. In order to study basic

factors related to angiogenesis and phenotypic changes of the capillaries located in tumor-bearing alveolar walls, we examined 37 primary lung adenocarcinomas with electron microscopy and confocal laser scanning microscopy with antibodies for TM, vWf, vascular endothelial growth factor (**VEGF**), and its receptors (KDR and Flt-1), and proliferating markers (Ki-67/proliferating cell nuclear antigen). Tissues microdissected specifically from alveolar walls were used for reverse transcription-polymerase chain reaction (RT-PCR) to assess expressions of mRNA isoforms of **VEGF** and its receptors. New capillary branching was found by ultrastructural study in the alveolar walls in 12% of the patients. Nuclei of the capillary endothelial cells were reactive for proliferating cell markers. Endothelial fenestrae were developed in 65% of the patients, TM reactivity was lost in the alveolar capillaries, and their cell cytoplasms obtained a reactivity for vWf through a transitional mosaic-like distribution pattern of both antigens. Besides cytoplasmic **VEGF** expression in neoplastic cells, tumor-bearing alveolar walls showed significant expression of mRNA of **VEGF165** and KDR. These findings imply that angiogenesis and phenotypic changes of the alveolar capillaries are closely related to a higher expression of tumor-associated **VEGF165** and of KDR in the alveolar walls in primary lung adenocarcinoma.

L6 ANSWER 5 OF 49 MEDLINE
ACCESSION NUMBER: 2001557197 MEDLINE
DOCUMENT NUMBER: 21489731 PubMed ID: 11603175
TITLE: [Platelet activation and endothelial factors in standard exercise test before and after menopause]. Aktywacja plytek i wybrane parametry funkcji srodblonka w trakcie standardowego wysilku fizycznego u kobiet w okresie okolomenopauzalnym.
AUTHOR: Krzysiek J; Milewicz T; Dybkowski R; Janczak-Saif A; Dembinska-Kiec A; Anna A Z; Guevara I; Sztefko K; Radowicki S; Dubiel J S; Klimek R
CORPORATE SOURCE: Katedra Endokrynologii i Plodnosci, Collegium Medicum, Uniwersytetu Jagiellonskiego w Krakowie.. mokrzysi@cyf-kr.edu.pl
SOURCE: PRZEGLAD LEKARSKI, (2001) 58 (5) 419-25. Journal code: 19840720R. ISSN: 0033-2240.
PUB. COUNTRY: Poland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Polish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011018
Last Updated on STN: 20020130
Entered Medline: 20020129

AB OBJECTIVES: Postmenopausal lack of estrogens may accelerate cardiovascular atheromatic changes. Standard exercise test (SET) challenges hidden signs of the vascular involvement. Although the test is known not to carry a risk of **thromboembolic** complications, it may influence plasma concentrations of endothelial and platelet factors. The question is if and to what extend the menopause aggravates the SET induced changes. AIM: Plasma concentrations of nitric oxide, endothelin-1, beta-**thromboglobulin** and von **Willebrand** factor activity before, at the maximum exercise and 15 minutes after the SET referred to, as a recovery time were estimated. METHOD: SET was performed according to Bruce protocol in group of 31 premenopausal and 57 postmenopausal women. Standard RIA kits for plasma beta-**thromboglobulin** (beta-TG) (Boehringer Mannheim) and endothelin-1 (Et-1) (Blotrack) concentration were used. The von **Willebrand** factor (vWF) activity was assayed by ELISA system (Boehringer Manheim). Plasma nitric oxide (NO) concentration was calculated from nitrides/nitrates levels, by Griess reaction, modified by use of NADPH reductase. RESULTS: Mean plasma levels of beta-TG, Et-1, NO and vWF activity do not differ between pre and postmenopausal women. The standard exercise test significantly increases both beta-TG plasma concentration and vWF activity ($p < 0.00001$). During the 15 minutes rest period the changed values do not return to preexercise levels. Neither plasma NO nor Et-1 plasma concentrations change during the exercise test. There was a similar increase in beta-TG plasma levels and vWF activity during the SET in pre- and postmenopausal women and a slighter increase of plasma Et-1 levels in postmenopausal women ($p < 0.04$). The close relationships between NO plasma concentration and both vWF activity ($p < 0.002$) and vascular endothelial growth factor (**VEGF**) level ($p < 0.04$) were observed in postmenopausal women. The vWF activity in postmenopausal; women inversely correlates with insulin-like growth factor-I (IGF-I) concentration ($p < 0.001$). In premenopausal women the important modulators of vWF activity were: body mass ($p < 0.04$), serum total cholesterol ($p < 0.02$) and sex hormone binding globulin (SHBG) levels ($p < 0.04$). The postmenopausal beta-TG increase during SET depends on body mass ($p < 0.02$), whereas the preexercise levels seem to be related to **VEGF** level ($p < 0.03$) and inversely to Et-1 ($p < 0.007$) and dehydroepiandrosterone sulfate (DHEAS) concentration ($p < 0.03$) Both the basal and stimulated by exercise vWF activity are higher in obese women ($p < 0.003$), but the net increase is larger in lean group (BMI < 30 kg/m2). In premenopausal women plasma NO concentration depends on 17 beta-estradiol serum level ($p < 0.02$). The higher **VEGF** ($p < 0.01$) levels as well as vWF activity was observed ($p < 0.03$) in hypercholesterolemic women. CONCLUSION: The standard exercise test increases the procoagulatory von **Willebrand** factor activity so as the platelets activity (beta-**thromboglobulin** concentration) in both pre and postmenopausal women. The slight endothelin-1 rise has been found at the maximum exercise in postmenopausal women. The close relation between plasma nitric oxide and endothelin-1 levels was found in postmenopausal women. Obesity and hypercholesterolemia may contribute to the observed changes.

L6 ANSWER 6 OF 49 MEDLINE
ACCESSION NUMBER: 2001296012 MEDLINE
DOCUMENT NUMBER: 21275843 PubMed ID: 11380837
TITLE: Venous neointimal hyperplasia in polytetrafluoroethylene dialysis grafts.
AUTHOR: Roy-Chaudhury P; Kelly B S; Miller M A; Reaves A; Armstrong J; Nanayakkara N; Heffelfinger S C
CORPORATE SOURCE: Division of Nephrology, Department of Medicine, University of Cincinnati, Cincinnati, Ohio 45267-0585, USA.. prabir.roychaudry@uc.edu
SOURCE: KIDNEY INTERNATIONAL, (2001 Jun) 59 (6) 2325-34. Journal code: KVB; 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

AB BACKGROUND: Vascular access dysfunction is the most important cause of morbidity and hospitalization in the hemodialysis population in the United States at a cost of $1 billion per annum. Venous neointimal hyperplasia (VNH) characterized by stenosis and subsequent **thrombosis** accounts for the overwhelming majority of pathology resulting in polytetrafluoroethylene (PTFE) dialysis graft failure. Despite the magnitude of the problem and the enormity of the cost ($1 billion), there are currently no effective therapies for the prevention or treatment of venous neointimal hyperplasia in PTFE dialysis grafts. METHODS: Tissue samples were collected from the graft-vein anastomosis of stenotic PTFE grafts during surgical revision. Specimens were graded using standard light microscopy and immunohistochemistry for the magnitude of neointimal hyperplasia and for the expression of specific cell types, cytokines, and matrix proteins. RESULTS: VNH was characterized by the (1) presence of smooth muscle cells/myofibroblasts, (2) accumulation of extracellular matrix components, (3) angiogenesis within the neointima and adventitia, and (4) presence of an active macrophage cell layer lining the PTFE graft material. Platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (**VEGF**) were expressed by smooth muscle cells/myofibroblasts within the venous neointima, by macrophages lining both sides of the PTFE graft, and by vessels within the neointima and adventitia. CONCLUSIONS: Our results suggest that macrophages, specific cytokines (bFGF, PDGF, and **VEGF**), and angiogenesis within the neointima and adventitia are likely to contribute to the pathogenesis of VNH in PTFE dialysis grafts. Interventions aimed at these specific mediators and processes may be successful in reducing the very significant human and economic costs of vascular access dysfunction.

L6 ANSWER 7 OF 49 MEDLINE
ACCESSION NUMBER: 2001222835 MEDLINE
DOCUMENT NUMBER: 21010833 PubMed ID: 11127848
TITLE: Systemic endothelial cell markers in primary antiphospholipid syndrome.
AUTHOR: Williams F M; Parmar K; Hughes G R; Hunt B J
CORPORATE SOURCE: Department of Haematology and Lupus Research, St Thomas' Hospital, London, UK.
SOURCE: THROMBOSIS AND HAEMOSTASIS, (2000 Nov) 84 (5) 742-6.
Journal code: VQ7; 7608063. ISSN: 0340-6245.
PUB. COUNTRY: Germany: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010502
Last Updated on STN: 20010502
Entered Medline: 20010426

AB The pathogenic mechanism underlying the prothrombotic tendency of Hughes' or antiphospholipid syndrome (APS) has not been elucidated. Numerous procoagulant mechanisms have been tested including platelet activation, monocyte tissue factor (TF) expression and endothelial cell (EC) activation. There is some evidence for the latter from studies on cultured human umbilical vein endothelial cells (HUVEC). Incubation with antiphospholipid antibodies (aPL) induces EC activation in vitro. We investigated whether there was evidence of EC perturbation in vivo using enzyme-linked immunosorbant assays (ELISAs) for soluble markers of EC dysfunction. Serum and plasma were collected from controls and patients with primary APS and ELISAs performed to quantify soluble vascular cell adhesion molecule (sVCAM), soluble intercellular adhesion molecule-1 (sICAM-1), interleukin-6 (IL-6), endothelin-1 (ET-1), von **Willebrand** factor (vWF) and soluble tissue factor (sTF). In addition, soluble p-selectin (p-selectin) and vascular endothelial growth factor (**VEGF**) were measured: the former as a marker of platelet activation, the latter as a potential mediator of TF expression. No significant differences in the levels of blood-borne soluble markers were detected between the patient and control groups except for **VEGF** and sTF, patients having significantly higher levels of **VEGF** and sTF than controls ($p < 0.05$). These results suggest plasma soluble tissue factor and **VEGF** may play a role in the pathogenesis of **thrombosis** in APS, although the cell of origin of these molecules remains unclear.

L6 ANSWER 8 OF 49 MEDLINE
ACCESSION NUMBER: 2001208763 MEDLINE
DOCUMENT NUMBER: 21196018 PubMed ID: 11297487
TITLE: Age-related macular degeneration is associated with increased vascular endothelial growth factor, hemorheology and endothelial dysfunction.
AUTHOR: Lip P L; Blann A D; Hope-Ross M; Gibson J M; Lip G Y
CORPORATE SOURCE: Haemostasis Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham B18 7QH, England, UK.
SOURCE: OPHTHALMOLOGY, (2001 Apr) 108 (4) 705-10.
Journal code: OI5; 7802443. ISSN: 0161-6420.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20010425
Entered Medline: 20010419

AB OBJECTIVE: To investigate laboratory evidence of abnormal angiogenesis, hemorheologic factors, endothelial damage/dysfunction, and age-related macular degeneration (ARMD). DESIGN: Comparative cross-sectional study. PARTICIPANTS: We studied 78 subjects (26 men and 52 women; mean age 74 years; standard deviation [SD] 9.0) with ARMD attending a specialist referral clinic. Subjects were compared with 25 healthy controls (mean age, 71 years; SD, 11). INTERVENTION AND OUTCOME MEASURES: Levels of vascular endothelial growth factor (**VEGF**, an index of angiogenesis), hemorheologic factors (plasma viscosity, hematocrit, white cell count, hemoglobin, platelets), fibrinogen (an index of rheology and hemostasis), and von **Willebrand** factor (a marker of endothelial dysfunction) were measured. RESULTS: Median plasma **VEGF** (225 vs. 195 pg/ml, $P = 0.019$) and mean von **Willebrand** factor (124 vs. 99 IU/dl, $P = 0.0004$) were greater in ARMD subjects than the controls. Mean plasma fibrinogen and plasma viscosity levels were also higher in the subjects (both $P < 0.0001$). There were no significant differences in other

indices between cases and controls. When "dry" (drusen, atrophy, n = 28) and "exudative" (n = 50) ARMD subjects were compared, there was no significant differences in **VEGF**, fibrinogen, viscosity, or von **Willebrand** factor levels. There were no significant correlations between the measured parameters. Stepwise multiple regression analysis did not demonstrate any significant clinical predictors (age, gender, smoking, body mass index, history of vascular disease, or hypertension) for plasma **VEGF** or fibrinogen levels, although smoking status was a predictor of plasma von **Willebrand** factor levels ($P < 0.05$). CONCLUSIONS: This study suggests an association between markers of angiogenesis (**VEGF**), hemorheologic factors, hemostasis, endothelial dysfunction, and ARMD. The interaction between abnormal angiogenesis and the components of Virchow's triad for **thrombogenesis** may in part contribute to the pathogenesis of ARMD.

L6 ANSWER 9 OF 49 MEDLINE
ACCESSION NUMBER: 2001029449 MEDLINE
DOCUMENT NUMBER: 20385503 PubMed ID: 10929208
TITLE: Endothelial-like cells derived from human CD14 positive monocytes.
AUTHOR: Fernandez Pujol B; Lucibello F C; Gehling U M; Lindemann K; Weidner N; Zuzarte M L; Adamkiewicz J; Elsasser H P; Muller R; Havemann K
CORPORATE SOURCE: Institute for Molecular Biology and Tumor Research (IMT), Philipps-University, Marburg, Germany.
SOURCE: DIFFERENTIATION, (2000 May) 65 (5) 287-300.
Journal code: E99. ISSN: 0301-4681.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001121

AB In the present study, we show that endothelial-like cells (ELCs) can develop from human CD14-positive mononuclear cells (CD14 cells) in the presence of angiogenic growth factors. The CD14 cells became loosely adherent within 24 h of culture and subsequently underwent a distinct process of morphological transformation to caudated or oval cells with eccentric nuclei. After 1 week in culture the cells showed a clear expression of endothelial cell markers, including von **Willebrand** factor (vWF), CD144 (VE-cadherin), CD105 (endoglin), acetylated low-density lipoprotein (AC-LDL)-receptor, CD36 (**thrombospondin** receptor), FLT-1, which is vascular endothelial cell growth factor (**VEGF**) receptor-1, and, to a weaker extent, KDR (**VEGF** receptor-2). Furthermore, in these cells structures resembling Weibel-Palade bodies at different storage stages were identified by electron microscopy, and upon culturing on three-dimensional fibrin gels the cells build network-like structures. In addition, cell proliferation and vWF expression was stimulated by **VEGF**, and the endothelial cell adhesion molecules CD54 (ICAM-1), and CD106 (VCAM-1) became transiently inducible by tumor necrosis factor-alpha (TNF-alpha). In contrast, the dendritic markers CD1a, and CD83 were not expressed to any significant extent. The expression of CD68, CD80 (B7-1), CD86 (B7-2), HLA-DR and CD36 may also suggest that ELCs might be related to macrophages, sinus lining or microvascular endothelial cells. Taken together, our observations indicate that ELCs can differentiate from cells of the monocytic lineage, suggesting a closer relationship between the monocyte/macrophage- and the endothelial cell systems than previously supposed.

L6 ANSWER 10 OF 49 MEDLINE
ACCESSION NUMBER: 2000190177 MEDLINE
DOCUMENT NUMBER: 20190177 PubMed ID: 10725978
TITLE: Elevated plasma vascular endothelial cell growth factor and **thrombomodulin** in juvenile diabetic patients.
AUTHOR: McLaren M; Elhadd T A; Greene S A; Belch J J
CORPORATE SOURCE: University Department of Medicine, Ninewells Hospital and Medical School, Dundee, Scotland, United Kingdom.
SOURCE: CLINICAL AND APPLIED THROMBOSIS/HEMOSTASIS, (1999 Jan) 5 (1) 21-4.
Journal code: DAV; 9508125. ISSN: 1076-0296.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000421
Last Updated on STN: 20000421
Entered Medline: 20000413

AB The major cause of morbidity and mortality in patients with type 1 diabetes mellitus is vascular disease and the death rate in this group of patients can be up to six times that of the general population. Elevated levels of blood glucose can cause endothelial cell damage, and markers of endothelial damage such as von **Willebrand** factor (vWF) and **thrombomodulin** (TM) have been reported to increase in adult diabetic patients. Growth factors are strongly linked to smooth muscle cell proliferation that contributes significantly to the vascular occlusive process and it has been shown that vascular endothelial cell growth factor (**VEGF**) stimulates release of vWF from endothelial cells. Vascular endothelial cell growth factor levels have been shown to be increased in vitreous fluid from the eyes of diabetic patients with proliferative retinopathy compared to those without. In this study we have shown that plasma levels of both TM and **VEGF** were significantly increased in juvenile diabetic patients with no clinical evidence of vascular disease compared to normal age and sex-matched control subjects. Median TM levels were 45.5 ng/mL (I.Q.R. 34 to 56 ng/mL) and 61 ng/mL (I.Q.R. 41 to 72 ng/mL) in the control group and in the diabetic patients respectively ($p = .0005$) and median levels of **VEGF** were 19.6 pg/mL (I.Q.R. 15.9 to 28.1 pg/mL) in the control group and 37.1 pg/mL (I.Q.R. 22.1 to 50.3 pg/mL) in the diabetic patients ($p = .027$ Mann-Whitney U test). This suggests that microvascular disease begins in childhood and can be detected using laboratory tests before any clinical changes are apparent.

L6 ANSWER 11 OF 49 MEDLINE
ACCESSION NUMBER: 1999342075 MEDLINE
DOCUMENT NUMBER: 99342075 PubMed ID: 10411932
TITLE: Regulation of vascular endothelial growth factor production and angiogenesis by the cytoplasmic tail of tissue factor.
AUTHOR: Abe K; Shoji M; Chen J; Bierhaus A; Danave I; Micko C;

Casper K; Dillehay D L; Nawroth P P; Rickles F R
CORPORATE SOURCE: Emory University School of Medicine, Atlanta, GA 30333, USA.
CONTRACT NUMBER: CA22202 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Jul 20) 96 (15) 8663-8.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990910
Last Updated on STN: 19990910
Entered Medline: 19990823

AB Tissue factor (TF), a transmembrane receptor for coagulation factor VII/VIIa, is aberrantly expressed in human cancers. We demonstrated a significant correlation between TF and vascular endothelial growth factor (**VEGF**) production in 13 human malignant melanoma cell lines ($r(2) = 0.869$, $P < 0.0001$). Two of these cell lines, RPMI-7951, a high TF and **VEGF** producer, and WM-115, a low TF and **VEGF** producer, were grown s.c. in severe combined immunodeficient mice. The high-producer cell line generated solid tumors characterized by intense vascularity, whereas the low producer generated relatively avascular tumors, as determined by immunohistologic staining of tumor vascular endothelial cells with anti-von **Willebrand** factor antibody. To investigate the structure-function relationship of TF and **VEGF**, a low-producer melanoma cell line (HT144) was transfected with a TF cDNA containing the full-length sequence, a cytoplasmic deletion mutant lacking the coding sequence for the distal three serine residues (potential substrates for protein kinase C), or an extracellular domain mutant, which has markedly diminished function for activation of factor X. Cells transfected with the full-length sequence produced increased levels of both TF and **VEGF**. Transfectants with the full-length sequence and the extracellular domain mutant produced approximately equal levels of **VEGF** mRNA. However, cells transfected with the cytoplasmic deletion mutant construct produced increased levels of TF, but little or no **VEGF**. Thus, the cytoplasmic tail of TF plays a role in the regulation of **VEGF** expression in some tumor cells.

L6 ANSWER 12 OF 49 MEDLINE
ACCESSION NUMBER: 95294232 MEDLINE
DOCUMENT NUMBER: 95294232 PubMed ID: 7775647
TITLE: Human chorionic gonadotropin-dependent expression of vascular endothelial growth factor/vascular permeability factor in human granulosa cells: importance in ovarian hyperstimulation syndrome.
AUTHOR: Neulen J; Yan Z; Raczek S; Weindel K; Keck C; Weich H A; Marme D; Breckwoldt M
CORPORATE SOURCE: Department of Obstetrics and Gynecology, University of Freiburg, Germany.
SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, (1995 Jun) 80 (6) 1967-71.
Journal code: HRB; 0375362. ISSN: 0021-972X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199507
ENTRY DATE: Entered STN: 19950720
Last Updated on STN: 19970203
Entered Medline: 19950707

AB Ovarian hyperstimulation syndrome (OHSS) is a severe complication arising from controlled ovarian stimulation treatment. This iatrogenic condition is potentially lethal and occurs in 0.3-5% of stimulated ovarian cycles. hCG exacerbates OHSS. The pathophysiology of OHSS is still unknown; therefore, treatment regimens are aimed at ameliorating symptoms. Prominent features of OHSS are an elevated risk of **thromboembolism** due to enhanced production of von **Willebrand** factor by endothelial cells and ascites, or pulmonary edema due to increased vascular permeability followed by third space fluid accumulation. Both of these sequelae can be evoked by vascular endothelial growth factor (**VEGF**), also known as vascular permeability factor (VPF). High concentrations of **VEGF**/VPF have been demonstrated in ascitic fluid from patients with OHSS, but the source of **VEGF**/VPF in these patients remained unidentified. Here we report that the messenger ribonucleic acid expression of **VEGF**/VPF in human luteinized granulosa cells (GCs) is dose and time dependently enhanced by hCG in vitro. Furthermore, **VEGF**/VPF proteins are produced by GCs. Our results suggest that the effects of hCG on the development and course of OHSS may be mediated by the production of **VEGF**/VPF by GCs.

L6 ANSWER 13 OF 49 MEDLINE
ACCESSION NUMBER: 94297320 MEDLINE
DOCUMENT NUMBER: 94297320 PubMed ID: 7517738
TITLE: Tumour angiogenesis.
AUTHOR: Le Querrec A; Duval D; Tobelem G
CORPORATE SOURCE: Laboratoire d'Hematologie, CHU, Caen, France.
SOURCE: BAILLIERES CLINICAL HAEMATOLOGY, (1993 Sep) 6 (3) 711-30.
Ref: 92
Journal code: BCH; 8800474. ISSN: 0950-3536.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940818
Last Updated on STN: 19960129
Entered Medline: 19940808

AB The progressive emergence of a close relationship between the formation of blood vessels in the vicinity of tumour cells and the development and spreading of tumours, strongly suggests that angiogenesis might be a prerequisite for tumour development. Angiogenesis starts and develops in response to two sets of extracellular signals: soluble angiogenic factors and extracellular matrix. Different experimental models have been used to study angiogenesis in vivo, but they have numerous limitations. Three-dimensional culture systems reconstitute normal interactions between endothelial cells and the surrounding extracellular matrix. Numerous parameters including angiogenic growth factors and cytokines, cell-to-cell interactions and cell-to-extracellular matrix adhesion influence the

growth and differentiation of endothelial cells in vitro as well as in vivo. Angiogenesis plays a major role not only in tumour growth but also in metastasis development. Mechanisms of switching to angiogenic phenotype have been recently described and onset of angiogenic activity is now recognized as another discrete step in tumorigenesis. Tumour cells can induce b-FGF expression and exportation, **VEGF** and **VEGF** receptor expression and inactivation of the cancer suppressor gene encoding for a fragment of **thrombospondin**. A controlled net proteolytic balance produced by tumour cells or endothelial cells is required to favour migration and invasion of endothelial cells and angiogenesis. The hypothesis that assessment of tumour angiogenesis might predict tumour aggressiveness in human cancer has recently gained support from several clinical studies. This has been shown for cutaneous melanoma, breast carcinoma, and non-small-cell lung cancer by quantitation of microvessels in human biopsies using von **Willebrand** factor or CD3 antigen labelling with specific antibodies. However, more specific and sensitive markers are needed to improve this approach for predicting tumour aggressiveness. Folkman proposed twenty years ago that inhibition of angiogenesis might represent a suitable complementary strategy for the treatment of various forms of cancer. Since then numerous angiostatic compounds have been identified but very few of them fit the required criteria of a potential drug. Fumagillin and particularly its synthetic analogue AGM 1470 might be developed for use in humans in the near future.

L6 ANSWER 14 OF 49 MEDLINE
ACCESSION NUMBER: 93184390 MEDLINE
DOCUMENT NUMBER: 93184390 PubMed ID: 7680247
TITLE: Epidermal growth factor stimulates vascular endothelial growth factor production by human malignant glioma cells: a model of glioblastoma multiforme pathophysiology.
AUTHOR: Goldman C K; Kim J; Wong W L; King V; Brock T; Gillespie G Y
CORPORATE SOURCE: Brain Tumor Research Laboratories, Division of Neurosurgery, University of Alabama, Birmingham 35294-0006.
CONTRACT NUMBER: HL-41180 (NHLBI)
NS31096 (NINDS)
T32NSO7335 (NINDS)
SOURCE: MOLECULAR BIOLOGY OF THE CELL, (1993 Jan) 4 (1) 121-33.
Journal code: BAU; 9201390. ISSN: 1059-1524.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930416
Last Updated on STN: 20000303
Entered Medline: 19930408

AB Hypervascularity, focal necrosis, persistent cerebral edema, and rapid cellular proliferation are key histopathologic features of glioblastoma multiforme (GBM), the most common and malignant of human brain tumors. By immunoperoxidase and immunofluorescence, we definitively have demonstrated the presence of vascular endothelial growth factor (**VEGF**) and epidermal growth factor receptor (EGFr) in five out of five human glioma cell lines (U-251MG, U-105MG, D-65MG, D-54MG, and CH-235MG) and in eight human GBM tumor surgical specimens. In vitro experiments with glioma cell lines revealed a consistent and reliable relation between EGFr activation and **VEGF** production; namely, EGF (1-20 ng/ml) stimulation of glioma cells resulted in a 25-125% increase in secretion of bioactive **VEGF**. Conditioned media (CM) prepared from EGF-stimulated glioma cell lines produced significant increases in cytosolic free intracellular concentrations of Ca2+ ([Ca2+]i) in human umbilical vein endothelial cells (HUVECs). Neither EGF alone or CM from glioma cultures prepared in the absence of EGF induced [Ca2+]i increases in HUVECs. Preincubation of glioma CM with A4.6.1, a monoclonal antibody to **VEGF**, completely abolished **VEGF**-mediated [Ca2+]i transients in HUVECs. Likewise, induction by glioma-derived CM of von **Willebrand** factor release from HUVECs was completely blocked by A4.6.1 pretreatment. These observations provide a key link in understanding the basic cellular pathophysiology of GBM tumor angiogenesis, increased vascular permeability, and cellular proliferation. Specifically, EGF activation of EGFr expressed on glioma cells leads to enhanced secretion of **VEGF** by glioma cells. **VEGF** released by glioma cells in situ most likely accounts for pathognomonic histopathologic and clinical features of GBM tumors in patients, including striking tumor angiogenesis, increased cerebral edema and hypercoagulability manifesting as focal tumor necrosis, deep vein **thrombosis**, or pulmonary embolism.

L6 ANSWER 15 OF 49 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:74641 CAPLUS
TITLE: Aerosol delivery of PEI-p53 complexes inhibits B16-F10 lung metastases through regulation of angiogenesis
AUTHOR(S): Gautam, Ajay; Densmore, Charles L.; Melton, Sara; Golunski, Eva; Waldrep, J. Clifford
CORPORATE SOURCE: Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, TX, 77030, USA
SOURCE: Cancer Gene Therapy (2002), 9(1), 28-36
CODEN: CGTHEG; ISSN: 0929-1903
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Inhibition of pulmonary metastases poses a difficult clin. challenge for current therapeutic regimens. We have developed an aerosol system utilizing a cationic polymer, polyethyleneimine (PEI), for topical gene delivery to the lungs as a novel approach for treatment of lung cancer. Using a B16-F10 murine melanoma model in C57BL/6 mice, we previously demonstrated that aerosol delivery of PEI-p53 DNA resulted in highly significant redns. in the tumor burden (P<.001) in treated animals, and also lead to about 50% increase in the mean length of survival of the mice-bearing B16-F10 lung tumors. The mechanisms of this antitumor effect of p53 are investigated in this report. Here, we demonstrate that the p53 transfection leads to an up-regulation of the antiangiogenic factor **thrombospondin**-1 (TSP-1) in the lung tissue and the serum of the mice. Furthermore, there is a down-regulation of vascular endothelial growth factor (**VEGF**) in the lung tissue and serum of the B16-F10 tumor-bearing mice treated with PEI-p53 DNA complexes, compared with untreated tumor-bearing animals. In addn., staining for von **Willebrand** factor (vWF), a marker for the angiogenic blood vessels, revealed that p53 treatment leads to a decrease in the angiogenic phenotype of the B16-F10 tumors. Immunohistochem. for transgene expression reveals that the PEI-p53 aerosol complexes transfect mainly the epithelial cells lining the airways, with diffuse transfection in the alveolar lining cells, as well as, the tumor foci in the lung tissue.

There was also some evidence of apoptosis in the lung tumor foci of animals treated with p53. The data suggest that aerosol delivery of PEI-p53 complexes leads to inhibition of B16-F10 lung metastases, in part by suppression of angiogenesis.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 49 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:825408 CAPLUS

TITLE: Angiogenesis and phenotypic alteration of alveolar capillary endothelium in areas of neoplastic cell spread in primary lung adenocarcinoma

AUTHOR(S): Jin, Enjing; Ghazizadeh, Mohammad; Fujiwara, Masakazu; Nagashima, Mikio; Shimizu, Hajime; Ohaki, Yoshiharu; Arai, Satoru; Gomibuchi, Makoto; Takemura, Tamiko; Kawanami, Oichi

CORPORATE SOURCE: Department of Molecular Pathology, Institute of Gerontology, Nippon Medical School, Kawasaki, 211-8533, Japan

SOURCE: Pathol. Int. (2001), 51(9), 691-700
CODEN: PITEES; ISSN: 1320-5463

PUBLISHER: Blackwell Science Asia Pty Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Normal alveolar capillary endothelium is quiescent in nature and displays anticoagulant **thrombomodulin** (TM) on its surface. The cytoplasms of these endothelial cells are ultrastructurally non-fenestrated type, and they barely express von **Willebrand** factor (vWf). Alveolar fibrosis is accompanied by a capillary endothelium reactive for vWf, and a loss of TM expression. In primary lung adenocarcinoma, neovascularization occurs in assocn. with alveolar fibrosis. In order to study basic factors related to angiogenesis and phenotypic changes of the capillaries located in tumor-bearing alveolar walls, we examd. 37 primary lung adenocarcinomas with electron microscopy and confocal laser scanning microscopy with antibodies for TM, vWf, vascular endothelial growth factor (**VEGF**), and its receptors (KDR and Flt-1), and proliferating markers (Ki-67/proliferating cell nuclear antigen). Tissues microdissected specifically from alveolar walls were used for reverse transcription-polymerase chain reaction (RT-PCR) to assess expressions of mRNA isoforms of **VEGF** and its receptors. New capillary branching was found by ultrastructural study in the alveolar walls in 12% of the patients. Nuclei of the capillary endothelial cells were reactive for proliferating cell markers. Endothelial fenestrae were developed in 65% of the patients, TM reactivity was lost in the alveolar capillaries, and their cell cytoplasms obtained a reactivity for vWf through a transitional mosaic-like distribution pattern of both antigens. Besides cytoplasmic **VEGF** expression in neoplastic cells, tumor-bearing alveolar walls showed significant expression of mRNA of **VEGF165** and KDR. These findings imply that angiogenesis and phenotypic changes of the alveolar capillaries are closely related to a higher expression of tumor-assocd. **VEGF165** and of KDR in the alveolar walls in primary lung adenocarcinoma.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 17 OF 49 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:894010 CAPLUS

DOCUMENT NUMBER: 134:161761

TITLE: Systemic endothelial cell markers in primary antiphospholipid syndrome

AUTHOR(S): Williams, Frances M. K.; Parmar, Kiran; Hughes, Graham R. V.; Hunt, Beverley J.

CORPORATE SOURCE: Departments of Haematology and Lupus Research, St Thomas' Hospital, London, SE1 7EH, UK

SOURCE: Thrombosis and Haemostasis (2000), 84(5), 742-746
CODEN: THHADQ; ISSN: 0340-6245

PUBLISHER: F. K. Schattauer Verlagsgesellschaft mbH

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The pathogenic mechanism underlying the prothrombotic tendency of Hughes' or anti-phospholipid syndrome (APS) has not been elucidated. Numerous procoagulant mechanisms have been tested including platelet activation, monocyte tissue factor (TF) expression and endothelial cell (EC) activation. There is some evidence for the latter from studies on cultured human umbilical vein endothelial cells (HUVEC). Incubation with anti-phospholipid antibodies (aPL) induces EC activation in vitro. The authors investigated whether there was evidence of EC perturbation in vivo using enzyme-linked immunosorbant assays (ELISAs) for sol. markers of EC dysfunction. Serum and plasma were collected from controls and patients with primary APS and ELISAs performed to quantify sol. vascular cell adhesion mol. (sVCAM), sol. intercellular adhesion mol.-1 (sICAM-1), interleukin-6 (IL-6), endothelin-1 (ET-1), von **Willebrand** factor (vWF) and sol. tissue factor (sTF). In addn., sol. P-selectin and vascular endothelial growth factor (**VEGF**) were measured: the former as a marker of platelet activation, the latter as a potential mediator of TF expression. No significant differences in the levels of blood-borne sol. markers were detected between the patient and control groups except for **VEGF** and sTF, patients having significantly higher levels of **VEGF** and sTF than controls. These results suggest plasma sol. tissue factor and **VEGF** may play a role in the pathogenesis of **thrombosis** in APS, although the cell of origin of these mols. remains unclear.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 18 OF 49 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:537179 CAPLUS

DOCUMENT NUMBER: 134:112391

TITLE: Endothelial-like cells derived from human CD14 positive monocytes

AUTHOR(S): Pujol, Beatriz Fernandez; Lucibello, Frances C.; Gehling, Ursula M.; Lindemann, Katharina; Weidner, Natalja; Zuzarte, Mary-Lou; Adamkiewicz, Jurgen; Elsasser, Hans-Peter; Muller, Rolf; Havemann, Klaus

CORPORATE SOURCE: Institute for Molecular Biology and Tumor Research (IMT), Philipps-University, Marburg, D-35033, Germany

SOURCE: Differentiation (Berlin) (2000), 65(5), 287-300
CODEN: DFFNAW; ISSN: 0301-4681

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In the present study, we show that endothelial-like cells (ELCs) can

develop from human CD14-pos. mononuclear cells (CD14 cells) in the presence of angiogenic growth factors. The CD14 cells became loosely adherent within 24 h of culture and subsequently underwent a distinct process of morphol. transformation to caudated or oval cells with eccentric nuclei. After 1 wk in culture the cells showed a clear expression of endothelial cell markers, including von **Willebrand** factor (vWF), CD144 (VE-cadherin), CD105 (endoglin), acetylated low-d. lipoprotein (AC-LDL)-receptor, CD36 (**thrombospondin** receptor), FLT-1, which is vascular endothelial cell growth factor (**VEGF**) receptor-1, and, to a weaker extent, KDR (**VEGF** receptor-2). Furthermore, in these cells structures resembling Weibel-Palade bodies at different storage stages were identified by electron microscopy, and upon culturing on three-dimensional fibrin gels the cells build network-like structures. In addn., cell proliferation and vWF expression was stimulated by **VEGF**, and the endothelial cell adhesion mols. CD54 (ICAM-1), and CD106 (VCAM-1) became transiently inducible by tumor necrosis factor-alpha (TNF-.alpha.). In contrast, the dendritic markers CD1a, and CD83 were not expressed to any significant extent. The expression of CD68, CD80 (B7-1), CD86 (B7-2), HLA-DR and CD36 may also suggest that ELCs might be related to macrophages, sinus lining or microvascular endothelial cells. Taken together, our observations indicate that ELCs can differentiate from cells of the monocytic lineage, suggesting a closer relationship between the monocyte/macrophage- and the endothelial cell systems than previously supposed.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 19 OF 49 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:606004 CAPLUS
DOCUMENT NUMBER: 132:135777
TITLE: Influence of LDL-apheresis on vascular endothelial growth factor (**VEGF165**), von **willebrand** factor (vWF) and beta **thromboglobulin** (.beta.-TG) levels in patients after PTCA or CABG
AUTHOR(S): Dembinska-Kiec, Aldona; Piwowarska, Wieslawa; Sinzinger, Helmut; Bartus, Stanislaw; Konduracka, Ewa; Golabek, Iwona; Hartwich, Jadwiga; Zdzienicka, Anna; Guevara, Ibeth; Dudek, Dariusz; Pietrzak, Izabella; Partyka, Lukasz; Sadowski, Jerzy; Dubiel, Jacek
CORPORATE SOURCE: Department of Clinical Biochemistry, Cardiovascular Department Jagiellonian University, Krakow, Pol.
SOURCE: Advances in Lipoprotein and Atherosclerosis Research, Diagnostics and Treatment, Proceedings of the International Dresden Lipid Symposium, 9th, June 27-29, 1997 (1998), Meeting Date 1997, 131-136. Editor(s): Hanefeld, Markolf. Fischer: Jena, Germany. CODEN: 68EPAR
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The authors obsd. that the blood vWB, **VEGF165** and .beta.-TG levels are significantly decreased after each LDL-apheresis procedure (dextran sulfate Kaneka columns), performed in 6 patients with severe coronary atherosclerosis on 2-3 days before and up to 3 mo after PTCA [percutaneous transluminal coronary angioplasty] or CABG [coronary artery bypass graft]. These data are in accordance with the results of LAARS [LDL-apheresis Atherosclerosis Regression Study] group, and suggest the improvement of endothelial function in patients undergoing the LDL-apheresis combined with statins treatment.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 20 OF 49 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:325811 CAPLUS
DOCUMENT NUMBER: 130:347887
TITLE: Regulators of PDGF-mediated microvascular communication and use in therapy
INVENTOR(S): Rosenberg, Robert D.; Edelberg, Jay M.; Aird, William C.
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA
SOURCE: PCT Int. Appl., 56 pp. CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9924059	A1	19990520	WO 1998-US23892	19981106
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9914541	A1	19990531	AU 1999-14541	19981106
PRIORITY APPLN. INFO.:			US 1997-64951P P	19971107
			WO 1998-US23892 W	19981106

AB PDGF AB-dependent regulation of endothelial cell gene expression, particularly in PDGF-.alpha. receptor pos. cardiac microvascular endothelial cells which constitutively express PDGF-A, is described, as well as methods of using the disclosed pathway to regulate endothelial cell development and function. The regulated genes express von **Willebrand** factor, **VEGF**, and Flk-1 and control endothelial cell proliferation, chemotactic migration, angiogenesis, neovascularization, **thrombosis** or fibrinolysis. Pharmaceutical compns. and methods of manufg. the agents of interest are also claimed. Factors that induce endothelial cell expression of PDGF-B are claimed; these factors are sol. factors produced by cardiac myocytes whose activity is neutralized by anti-EGF antibodies. More specifically, the sol. factor is exogenous PDGF-AB. Agents that block PDGF-AB binding to endothelial cell PDGF-.alpha. receptors for use in therapy are also claimed. This blocking agent is an antibody, or functional portion of an antibody, characterized by binding to an epitope present in the group of polypeptide chains consisting of PDGF-A, PDGF-B, PDGF-.alpha. receptor and PDGF-.beta. receptor or an epitope created by the formation of PDGF dimeric ligands. A method of evaluating a candidate substance for its ability to regulate the interaction of PDGF-AB with PDGF-.alpha. receptors expressed on microvascular endothelial is also claimed.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 21 OF 49 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:617533 CAPLUS
TITLE: Human chorionic gonadotropin-dependent expression of vascular endothelial growth factor/vascular permeability factor in human granulosa cells: importance in ovarian hyperstimulation syndrome
AUTHOR(S): Neulen, Joseph; Yan, Zhaoping; Raczek, Sonja; Weindel, Karin; Keck, Christoph; Weich, Herbert A.; Marme, Dieter; Breckwoldt, Meinert
CORPORATE SOURCE: Department of Obstetrics and Gynecology, University of Freiburg, Freiburg, 79106, Germany
SOURCE: J. Clin. Endocrinol. Metab. (1995), 80(6), 1967-71
CODEN: JCEMAZ; ISSN: 0021-972X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ovarian hyperstimulation syndrome (OHSS) is a serve complication arising from controlled ovarian stimulation treatment. This iatrogenic condition is potentially lethal and occurs in 0.3-5% of stimulated ovarian cycles. HCG exacerbates OHSS. The pathophysiol. of OHSS is still unknown; therefore, treatment regimens are aimed at ameliorating symptoms. Prominent features of OHSS are an elevated risk of **thromboembolism** due to enhanced prodn. of von **Willebrand** factor by endothelial cells and ascites, or pulmonary edema due to increased vascular permeability followed by third space fluid accumulation. Both of these sequelae can be evoked by vascular endothelial growth factor (**VEGF**), also known as vascular permeability factor (VPF). High concns. of **VEGF**/VPF have been demonstrated in ascitic fluid from patients with OHSS, but the source of **VEGF**/VPF in these patients remained unidentified. Here we report that the mRNA expression of **VEGF** /VPF in human luteinized granulosa cells (GCs) is dose and time dependently enhanced by hCG in vitro. Furthermore, **VEGF**/VPF proteins are produced by GCs. Our results suggest that the effects of hCG on the development and course of OHSS may be mediated by the prodn. of **VEGF**/VPF by GCs.

L6 ANSWER 22 OF 49 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:210425 CAPLUS
DOCUMENT NUMBER: 118:210425
TITLE: Epidermal growth factor stimulates vascular endothelial growth factor production by human malignant glioma cells: A model of glioblastoma multiforme pathophysiology
AUTHOR(S): Goldman, Corey K.; Kim, Jin; Wong, Wai Lee; King, Vickie; Brock, Tommy; Gillespie, G. Yancey
CORPORATE SOURCE: Dep. Surg. Vasc. Biol., Univ. Alabama, Birmingham, AL, 35294-0006, USA
SOURCE: Mol. Biol. Cell (1993), 4(1), 121-33
CODEN: MBCEEV; ISSN: 1059-1524
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hypervascularity, focal necrosis, persistent cerebral edema, and rapid cellular proliferation are key histopathol. features of glioblastoma multiforme (GBM), the most common and malignant of human brain tumors. By immunoperoxidase and immunofluorescence, we have definitively demonstrated the presence of vascular endothelial growth factor (**VEGF**) and epidermal growth factor receptor (EGFr) in five out of five human glioma cell lines (U-251MG, U-105MG, D-65MG, D-54MG, and CH-235MG) and in eight human GBM tumor surgical specimens. In vitro expts. with glioma cell lines revealed a consistent and reliable relation between EGFr activation and **VEGF** prodn.; namely, EGF (1-20 ng/mL) stimulation of glioma cells resulted in a 25-125% increase in secretion of bioactive **VEGF**. Conditioned media (CM) prepd. from EGF-stimulated glioma cell lines produced significant increases in cytosolic free intracellular concns. of Ca2+ ([Ca2+]i) in human umbilical vein endothelial cells (HUVECs). Neither EGF alone or CM from glioma cultures prepd. in the absence of EGF induced [Ca2+]i increases in HUVECs. Preincubation of glioma CM with A4.6.1, a monoclonal antibody to **VEGF**, completely abolished **VEGF**-mediated [Ca2+]i transients in HUVECs. Likewise, induction by glioma-derived CM of von **Willebrand** factor release from HUVECs was completely blocked by A4.6.1 pretreatment. These observations provide a key link in understanding the basic cellular pathophysiol. of GBM tumor angiogenesis, increased vascular permeability, and cellular proliferation. Specifically, EGF activation of EGFr expressed on glioma cells leads to enhanced secretion of **VEGF** by glioma cells. **VEGF** released by glioma cells in situ most likely accounts for pathognomonic histopathol. and clin. features of GBM tumors in patients, including striking tumor angiogenesis, increased cerebral edema and hypercoagulability manifesting as focal tumor necrosis, deep vein **thrombosis**, or pulmonary embolism.

L6 ANSWER 23 OF 49 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002110213 EMBASE
TITLE: Analysis of intrapulmonary vessels and epithelial-endothelial interactions in the human developing lung.
AUTHOR: Maeda S.; Suzuki S.; Suzuki T.; Endo M.; Moriya T.; Chida M.; Kondo T.; Sasano H.
CORPORATE SOURCE: Dr. S. Maeda, Department of Thoracic Surgery, Inst. of Development, Aging and Can., Tohoku University, 4-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan. sumiko@idac.tohoku.ac.jp
SOURCE: Laboratory Investigation, (2002) 82/3 (293-301).
Refs: 38
ISSN: 0023-6837 CODEN: LAINAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
021 Developmental Biology and Teratology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The establishment of a sufficiently wide and functional blood-gas interface is of critical importance in lung development, but development of the intrapulmonary vascular system including alveolar capillary vessels still remains unclear. In this study, we first characterized the structural development of the vascular system in accordance with that of airways in human fetal lungs at the pseudoglandular phase (8, 13, and 16 weeks gestation) by examining the immunohistochemical distribution of CD34 and .alpha.-smooth muscle actin (SMA). Using double immunohistochemistry and 3-dimensional reconstruction techniques, endothelial cells in the

developing lung could be classified into two different types according to the characteristics of their adjacent cells (presence or absence of SMA-positive cells) and their distribution (proximal or distal lung parenchyme). Endothelial cells without SMA-positive cells developed into a capillary network surrounding the budding components of distal airways during the mid-pseudoglandular phase before communicating with proximal vessels. We then examined the immunoreactivity of **thrombomodulin** and von **Willebrand** factor (vWF) in endothelial cells. Endothelial cells of the capillary network were mainly positive for vWF during the early gestational stages, but altered their phenotypes to those of mature lungs (vWF negative and **thrombomodulin** positive) during the terminal sac phase. We subsequently determined the immunohistochemical distribution of vascular endothelial growth factor (**VEGF**). Epithelial cells of the most distal airways were intensely positive for **VEGF**. These results suggest that **VEGF** present in airway epithelial cells is involved in the maturation as well as proliferation of capillary endothelial cells. Epithelial-endothelial interactions during lung development are considered very important in the establishment of the functional blood-gas interface.

L6 ANSWER 24 OF 49 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002084243 EMBASE
TITLE: Biochemical parameters of endothelial dysfunction in cardiological syndrome X.
AUTHOR: Kolasinska-Kloch W.; Lesniak W.; Kiec-wilk B.; Malczewska-Malec M.
CORPORATE SOURCE: W. Lesniak, Department of Cardiology, ul. Kopernika 17, 31-501 Krakow, Poland. wiktorialesniak@cracow.pl
SOURCE: Scandinavian Journal of Clinical and Laboratory Investigation, (2002) 62/1 (7-14).
Refs: 39
ISSN: 0036-5513 CODEN: SJCLAY
COUNTRY: Norway
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The endothelial dysfunction in cardiological syndrome X has been studied mainly by invasive methods and by measuring vasoactive mediator (nitric oxide (NO), endothelin-1) levels. Other parameters evaluating this dysfunction (defined as an imbalance between vascular relaxing and contracting factors, between procoagulant and anticoagulant or growth-inhibiting and growth-promoting substances) have not been used. Methods: Twenty-five non-diabetic patients (16 men, 9 women) with cardiological syndrome X and 10 healthy volunteers (5 men, 5 women) were examined. Biochemical parameters: ET-1, the end products of nitric oxide metabolism (NO(x)), **VEGF**, vWF, .beta.TG, tPA, PAI-1 were measured before and during an ECG exercise tolerance test. The blood concentrations of testosterone and estradiol in men and LH, FSH and estradiol in women were tested. Results: A significantly lower basal concentration of NO(x) ($p = 0.01$), lower basal NO(x)/ET-1 ratio ($p<0.05$) and higher levels of **VEGF** ($p<0.05$) were observed in patients with cardiological syndrome X. The male patients also had higher concentrations of estradiol ($p<0.05$). A significant decrease in tPA concentration and increase in .beta.TG was noticed during exercise, but with no differences between the study groups. Conclusions: Endothelial dysfunction in cardiological syndrome X manifests mainly in the regulation of vessel wall tonus, which was revealed by the decrease of NO(x) level and NO(x)/ET-1 ratio. **VEGF** elevation in syndrome X may result from chronic tissue ischaemia due to endothelial dysfunction. Exercise augments the prothrombotic activity of the blood, since a significant elevation in .beta.TG and decrease in tPA were observed after exercise.

L6 ANSWER 25 OF 49 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002023359 EMBASE
TITLE: Aerosol delivery of PEI-p53 complexes inhibits B16-F10 lung metastases through regulation of angiogenesis.
AUTHOR: Gautam A.; Densmore C.L.; Melton S.; Golunski E.; Waldrep J.C.
CORPORATE SOURCE: Dr. J.C. Waldrep, Department of Molecular Physiology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, United States. jwaldrep@bcm.imc.edu
SOURCE: Cancer Gene Therapy, (2002) 9/1 (28-36).
Refs: 32
ISSN: 0929-1903 CODEN: CGTHEG
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Inhibition of pulmonary metastases poses-a-difficult-clinical challenge for current therapeutic regimens. We have developed an aerosol system utilizing a cationic polymer, polyethyleneimine (PEI), for topical gene delivery to the lungs as a novel approach for treatment of lung cancer. Using a B16-F10 murine melanoma model in C57BL/6 mice, we previously demonstrated that aerosol delivery of PEI-p53 DNA resulted in highly significant reductions in the tumor burden ($P<.001$) in treated animals, and also lead to about 50% increase in the mean length of survival of the mice-bearing B16-F10 lung tumors. The mechanisms of this antitumor effect of p53 are investigated in this report. Here, we demonstrate that the p53 transfection leads to an up-regulation of the antiangiogenic factor **thrombospondin**-1 (TSP-1) in the lung tissue and the serum of the mice. Furthermore, there is a down-regulation of vascular endothelial growth factor (**VEGF**) in the lung tissue and serum of the B16-F10 tumor-bearing mice treated with PEI-p53 DNA complexes, compared with untreated tumor-bearing animals. In addition, staining for von **Willebrand** factor (vWF), a marker for the angiogenic blood vessels, revealed that p53 treatment leads to a decrease in the angiogenic phenotype of the B16-F10 tumors. Immunohistochemistry for transgene expression reveals that the PEI-p53 aerosol complexes transfect mainly the epithelial cells lining the airways, with diffuse transfection in the alveolar lining cells, as well as, the tumor foci in the lung tissue. There was also some evidence of apoptosis in the lung tumor foci of animals treated with p53. The data suggest that aerosol delivery of PEI-p53 complexes leads to inhibition of B16-F10 lung metastases, in part by suppression of angiogenesis.

L6 ANSWER 26 OF 49 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001375221 EMBASE
TITLE: Angiogenesis and phenotypic alteration of alveolar capillary endothelium in areas of neoplastic cell spread in primary lung adenocarcinoma.
AUTHOR: Jin E.; Ghazizadeh M.; Fujiwara M.; Nagashima M.; Shimizu H.; Ohaki Y.; Arai S.; Gomibuchi M.; Takemura T.; Kawanami O.
CORPORATE SOURCE: Dr. O. Kawanami, Department of Molecular Pathology, Institute of Gerontology, Nippon Medical School, 1-396 Kosugi-cho, Kanagawa-ken 211-8533, Japan. kawanami/ig@nms.ac.jp
SOURCE: Pathology International, (2001) 51/9 (691-700). Refs: 33 ISSN: 1320-5463 CODEN: PITEES
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Normal alveolar capillary endothelium is quiescent in nature and displays anticoagulant **thrombomodulin** (TM) on its surface. The cytoplasms of these endothelial cells are ultra-structurally non-fenestrated type, and they barely express von **Willebrand** factor (vWf). Alveolar fibrosis is accompanied by a capillary endothelium reactive for vWf, and a loss of TM expression. In primary lung adenocarcinoma, neovas-cularization occurs in association with alveolar fibrosis. In order to study basic factors related to angiogenesis and phenotypic changes of the capillaries located in tumor-bearing alveolar walls, we examined 37 primary lung adeno-carcinomas with electron microscopy and confocal laser scanning microscopy with antibodies for TM, vWf, vascular endothelial growth factor (**VEGF**), and its receptors (KDR and Flt-1), and proliferating markers (Ki-67/proliferating cell nuclear antigen). Tissues microdissected specifically from alveolar walls were used for reverse transcription-polymerase chain reaction (RT-PCR) to assess expressions of mRNA isoforms of **VEGF** and its receptors. New capillary branching was found by ultrastructural study in the alveolar walls in 12% of the patients. Nuclei of the capillary endo-thelial cells were reactive for proliferating cell markers. Endothelial fenestrae were developed in 65% of the patients, TM reactivity was lost in the alveolar capillaries, and their cell cytoplasms obtained a reactivity for vWf through a transitional mosaic-like distribution pattern of both antigens. Besides cytoplasmic **VEGF** expression in neoplastic cells, tumor-bearing alveolar walls showed significant expression of mRNA of **VEGF**(165) and KDR. These findings imply that angiogenesis and phenotypic changes of the alveolar capillaries are closely related to a higher expression of tumor-associated **VEGF**(165) and of KDR in the alveolar walls in primary lung adenocarcinoma.

L6 ANSWER 27 OF 49 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001115817 EMBASE
TITLE: Age-related macular degeneration is associated with increased vascular endothelial growth factor, hemorheology and endothelial dysfunction.
AUTHOR: Lip P.-L.; Blann A.D.; Hope-Ross M.; Gibson J.M.; Lip G.Y.H.
CORPORATE SOURCE: Dr. G.Y.H. Lip, University Department of Medicine, City Hospital, Birmingham B18 7QH, United Kingdom
SOURCE: Ophthalmology, (2001) 108/4 (705-710). Refs: 24 ISSN: 0161-6420 CODEN: OPHTDG
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objective: To investigate laboratory evidence of abnormal angiogenesis, hemorheologic factors, endothelial damage/dysfunction, and age-related macular degeneration (ARMD). Design: Comparative cross-sectional study. Participants: We studied 78 subjects (26 men and 52 women; mean age 74 years; standard deviation [SD] 9.0) with ARMD attending a specialist referral clinic. Subjects were compared with 25 healthy controls (mean age, 71 years; SD, 11). Intervention and Outcome Measures: Levels of vascular endothelial growth factor (**VEGF**, an index of angiogenesis), hemorheologic factors (plasma viscosity, hematocrit, white cell count, hemoglobin, platelets), fibrinogen (an index of rheology and hemostasis), and von **Willebrand** factor (a marker of endothelial dysfunction) were measured. Results: Median plasma **VEGF** (225 vs. 195 pg/ml, P = 0.019) and mean von **Willebrand** factor (124 vs. 99 IU/dl, P = 0.0004) were greater in ARMD subjects than the controls. Mean plasma fibrinogen and plasma viscosity levels were also higher in the subjects (both P < 0.0001). There were no significant differences in other indices between cases and controls. When "dry" (drusen, atrophy, n = 28) and "exudative" (n = 50) ARMD subjects were compared, there was no significant differences in **VEGF**, fibrinogen, viscosity, or von **Willebrand** factor levels. There were no significant correlations between the measured parameters. Stepwise multiple regression analysis did not demonstrate any significant clinical predictors (age, gender, smoking, body mass index, history of vascular disease, or hypertension) for plasma **VEGF** or fibrinogen levels, although smoking status was a predictor of plasma von **Willebrand** factor levels (P < 0.05). Conclusions: This study suggests an association between markers of angiogenesis (**VEGF**), hemorheologic factors, hemostasis, endothelial dysfunction, and ARMD. The interaction between abnormal angiogenesis and the components of Virchow's triad for **thrombogenesis** may in part contribute to the pathogenesis of ARMD. .COPYRGT. 2001 by the American Academy of Ophthalmology.

L6 ANSWER 28 OF 49 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000415643 EMBASE
TITLE: Systemic endothelial cell markers in primary antiphospholipid syndrome.
AUTHOR: Williams P.M.K.; Parmar K.; Hughes G.R.V.; Hunt B.J.
CORPORATE SOURCE: Dr. B.J. Hunt, Department of Haematology, 4th Floor North Wing, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, United Kingdom. Beverley.hunt@gstt.sthames.nhs.uk
SOURCE: Thrombosis and Haemostasis, (2000) 84/5 (742-746). Refs: 35 ISSN: 0340-6245 CODEN: THHADQ
COUNTRY: Germany

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
005 General Pathology and Pathological Anatomy
025 Hematology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The pathogenic mechanism underlying the prothrombotic tendency of Hughes' or antiphospholipid syndrome (APS) has not been elucidated. Numerous procoagulant mechanisms have been tested including platelet activation, monocyte tissue factor (TF) expression and endothelial cell (EC) activation. There is some evidence for the latter from studies on cultured human umbilical vein endothelial cells (HUVEC). Incubation with antiphospholipid antibodies (aPL) induces EC activation in vitro. We investigated whether there was evidence of EC perturbation in vivo using enzyme-linked immunosorbant assays (ELISAs) for soluble markers of EC dysfunction. Serum and plasma were collected from controls and patients with primary APS and ELISAs performed to quantify soluble vascular cell adhesion molecule (sVCAM), soluble intercellular adhesion molecule-1 (sICAM-1), interleukin-6 (IL-6), endothelin-1 (ET-1), von **Willebrand** factor (vWF) and soluble tissue factor (sTF). In addition, soluble p-selectin (p-selectin) and vascular endothelial growth factor (**VEGF**) were measured: The former as a marker of platelet activation, the latter as a potential mediator of TF expression. No significant differences in the levels of blood-borne soluble markers were detected between the patient and control groups except for **VEGF** and sTF, patients having significantly higher levels of **VEGF** and sTF than controls (P<0.05). These results suggest plasma soluble tissue factor and **VEGF** may play a role in the pathogenesis of **thrombosis** in APS, although the cell of origin of these molecules remains unclear.

L6 ANSWER 29 OF 49 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000217783 EMBASE
TITLE: Endothelial-like cells derived from human CD14 positive monocytes.
AUTHOR: Fernandez Pujol B.; Lucibello F.C.; Gehling U.M.; Lindemann K.; Weidner N.; Zuzarte M.-L.; Adamkiewicz J.; Elsasser H.-P.; Muller R.; Havemann K.
CORPORATE SOURCE: K. Havemann, Inst. Mol. Biology Tumor Res., Philipps-University, Emil-Mannkopff-Strasse 2, D-35033 Marburg, Germany. havemann@imt.uni-marburg.de
SOURCE: Differentiation, (2000) 65/5 (287-300).
Refs: 45
ISSN: 0301-4681 CODEN: DFFNAW
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 021 Developmental Biology and Teratology
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In the present study, we show that endothelial-like cells (ELCs) can develop from human CD14-positive mononuclear cells (CD14 cells) in the presence of angiogenic growth factors. The CD14 cells became loosely adherent within 24 h of culture and subsequently underwent a distinct process of morphological transformation to caudated or oval cells with eccentric nuclei. After 1 week in culture the cells showed a clear expression of endothelial cell markers, including von **Willebrand** factor (vWF), CD144 (VE-cadherin), CD105 (endoglin), acetylated low-density lipoprotein (AC-LDL)-receptor, CD36 (**thrombospondin** receptor), FLT-1, which is vascular endothelial cell growth factor (**VEGF**) receptor-1, and, to a weaker extent, KDR (**VEGF** receptor-2). Furthermore, in these cells structures resembling Weibel-Palade bodies at different storage stages were identified by electron microscopy, and upon culturing on three-dimensional fibrin gels the cells build network-like structures. In addition, cell proliferation and vWF expression was stimulated by **VEGF**, and the endothelial cell adhesion molecules CD54 (ICAM-1), and CD106 (VCAM-1) became transiently inducible by tumor necrosis factor-alpha (TNF-.alpha.). In contrast, the dendritic markers CD1a, and CD83 were not expressed to any significant extent. The expression of CD68, CD80 (B7-1), CD86 (B7-2), HLA-DR and CD36 may also suggest that ELCs might be related to macrophages, sinus lining or microvascular endothelial cells. Taken together, our observations indicate that ELCs can differentiate from cells of the monocytic lineage, suggesting a closer relationship between the monocyte/macrophage- and the endothelial cell systems than previously supposed.

L6 ANSWER 30 OF 49 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999264596 EMBASE
TITLE: Regulation of vascular endothelial growth factor production and angiogenesis by the cytoplasmic tail of tissue factor.
AUTHOR: Abe K.; Shoji M.; Chen J.; Bierhaus A.; Danave I.; Micko C.; Casper K.; Dillehay D.L.; Nawroth P.P.; Rickles F.R.
CORPORATE SOURCE: M. Shoji, Division of Hematology/Oncology, Department of Medicine, Emory University, 1639 Pierce Drive, Atlanta, GA 30322, United States. mslaoji@emory.edu
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (20 Jul 1999) 96/15 (8663-8668).
Refs: 26
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Tissue factor (TF), a transmembrane receptor for coagulation factor VII/VIIa, is aberrantly expressed in human cancers. We demonstrated a significant correlation between TF and vascular endothelial growth factor (**VEGF**) production in 13 human malignant melanoma cell lines (r2 = 0.869, P < 0.0001). Two of these cell lines, RPMI-7951, a high TF and **VEGF** producer, and WM-115, a low TF and **VEGF** producer, were grown s.c. in severe combined immunodeficient mice. The high-producer cell line generated solid tumors characterized by intense vascularity, whereas the low producer generated relatively avascular tumors, as determined by immunohistologic staining of tumor vascular endothelial cells with anti-von **Willebrand** factor antibody. To investigate the structure-function relationship of TF and **VEGF**, a low-producer melanoma cell line (HT144) was transfected with a TF cDNA

containing the full-length sequence, a cytoplasmic deletion mutant lacking the coding sequence for the distal three serine residues (potential substrates for protein kinase C), or an extracellular domain mutant, which has markedly diminished function for activation of factor X. Cells transfected with the full-length sequence produced increased levels of both TF and **VEGF**. Transfectants with the full-length sequence and the extracellular domain mutant produced approximately equal levels of **VEGF** mRNA. However, cells transfected with the cytoplasmic deletion mutant construct produced increased levels of TF, but little or no **VEGF**. Thus, the cytoplasmic tail of TF plays a role in the regulation of **VEGF** expression in some tumor cells.

L6 ANSWER 31 OF 49 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999021948 EMBASE
TITLE: Elevated plasma vascular endothelial cell growth factor and **thrombomodulin** in juvenile diabetic patients.
AUTHOR: McLaren M.; Elhadd T.A.; Greene S.A.; Belch J.J.F.
CORPORATE SOURCE: Dr. M. McLaren, Department of Medicine, Ninewells Hosp. and Medical School, Dundee DD1 9SY, United Kingdom
SOURCE: Clinical and Applied Thrombosis/Hemostasis, (1999) 5/1 (21-24).
Refs: 21
ISSN: 1076-0296 CODEN: CATHF
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The major cause of morbidity and mortality in patients with type 1 diabetes mellitus is vascular disease and the death rate in this group of patients can be up to six times that of the general population. Elevated levels of blood glucose can cause endothelial cell damage, and markers of endothelial damage such as von **Willebrand** factor (vWF) and **thrombomodulin** (TM) have been reported to increase in adult diabetic patients. Growth factors are strongly linked to smooth muscle cell proliferation that contributes significantly to the vascular occlusive process and it has been shown that vascular endothelial cell growth factor (**VEGF**) stimulates release of vWF from endothelial cells. Vascular endothelial cell growth factor levels have been shown to be increased in vitreous fluid from the eyes of diabetic patients with proliferative retinopathy compared to those without. In this study we have shown that plasma levels of both TM and **VEGF** were significantly increased in juvenile diabetic patients with no clinical evidence of vascular disease compared to normal age and sex-matched control subjects. Median TM levels were 45.5 ng/mL (I.Q.R. 34 to 56 ng/mL) and 61 ng/mL (I.Q.R. 41 to 72 ng/mL) in the control group and in the diabetic patients respectively (p = .0005) and median levels of **VEGF** were 19.6 pg/mL (I.Q.R. 15.9 to 28.1 pg/mL) in the control group and 37.1 pg/mL (I.Q.R. 22.1 to 50.3 pg/mL) in the diabetic patients (p = .027 Mann-Whitney U test). This suggests that microvascular disease begins in childhood and can be detected using laboratory tests before any clinical changes are apparent.

L6 ANSWER 32 OF 49 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95181812 EMBASE
DOCUMENT NUMBER: 1995181812
TITLE: Human chorionic gonadotropin-dependent expression of vascular endothelial growth factor/vascular permeability factor in human granulosa cells: Importance in ovarian hyperstimulation syndrome.
AUTHOR: Neulen J.; Yan Z.; Raczek S.; Weindel K.; Keck C.; Weich H.A.; Marme D.; Breckwoldt A.
CORPORATE SOURCE: Department of Obstetrics/Gynecology, University of Freiburg, Hugstetter Strasse 55,79106 Freiburg, Germany
SOURCE: Journal of Clinical Endocrinology and Metabolism, (1995) 80/6 (1967-1971).
ISSN: 0021-972X CODEN: JCEMAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
010 Obstetrics and Gynecology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Ovarian hyperstimulation syndrome (OHSS) is a severe complication arising from controlled ovarian stimulation treatment. This iatrogenic condition is potentially lethal and occurs in 0.3-5% of stimulated ovarian cycles. hCG exacerbates OHSS. The pathophysiology of OHSS is still unknown; therefore, treatment regimens are aimed at ameliorating symptoms. Prominent features of OHSS are an elevated risk of **thromboembolism** due to enhanced production of yon **Willebrand** factor by endothelial cells and ascites, or pulmonary edema due to increased vascular permeability followed by third space fluid accumulation. Both of these sequelae can be evoked by vascular endothelial growth factor (**VEGF**), also known as vascular permeability factor (VPF). High concentrations of **VEGF**/VPF have been demonstrated in ascitic fluid from patients with OHSS, but the source of **VEGF**/VPF in these patients remained unidentified. Here we report that the messenger ribonucleic acid expression of **VEGF**/VPF in human luteinized granulosa cells (GCs) is dose and time dependently enhanced by hCG in vitro. Furthermore, **VEGF**/VPF proteins are produced by GCs. Our results suggest that the effects of hCG on the development and course of OHSS may be mediated by the production of **VEGF**/VPF by GCs.

L6 ANSWER 33 OF 49 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93306601 EMBASE
DOCUMENT NUMBER: 1993306601
TITLE: Tumour angiogenesis.
AUTHOR: Le Querrec A.; Duval D.; Tobelem G.
CORPORATE SOURCE: Biology Dept, Laboratoire d'Hematologie, CHU, Avenue de la Cote de Nacre,14000 Caen, France
SOURCE: Bailliere's Clinical Haematology, (1993) 6/3 (711-730).
ISSN: 0950-3536 CODEN: BCHAEW
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
025 Hematology
037 Drug Literature Index
LANGUAGE: English

SUMMARY LANGUAGE: English

AB The progressive emergence of a close relationship between the formation of blood vessels in the vicinity of tumour cells and the development and spreading of tumours, strongly suggests that angiogenesis might be a prerequisite for tumour development. Angiogenesis starts and develops in response to two sets of extracellular signals: soluble angiogenic factors and extracellular matrix. Different experimental models have been used to study angiogenesis in vivo, but they have numerous limitations. Three-dimensional culture systems reconstitute normal interactions between endothelial cells and the surrounding extracellular matrix. Numerous parameters including angiogenic growth factors and cytokines, cell-to-cell interactions and cell-to-extracellular matrix adhesion influence the growth and differentiation of endothelial cells in vitro as well as in vivo. Angiogenesis plays a major role not only in tumour growth but also in metastasis development. Mechanisms of switching to angiogenic phenotype have been recently described and onset of angiogenic activity is now recognized as another discrete step in tumorigenesis. Tumour cells can induce b-FGF expression and exportation, **VEGF** and **VEGF** receptor expression and inactivation of the cancer suppressor gene encoding for a fragment of **thrombospondin**. A controlled net proteolytic balance produced by tumour cells or endothelial cells is required to favour migration and invasion of endothelial cells and angiogenesis. The hypothesis that assessment of tumour angiogenesis might predict tumour aggressiveness in human cancer has recently gained support from several clinical studies. This has been shown for cutaneous melanoma, breast carcinoma, and non-small-cell lung cancer by quantitation of microvessels in human biopsies using von **Willebrand** factor or CD 3 antigen labelling with specific antibodies. However, more specific and sensitive markers are needed to improve this approach for predicting tumour aggressiveness. Folkman proposed twenty years ago that inhibition of angiogenesis might represent a suitable complementary strategy for the treatment of various forms of cancer. Since then numerous angiostatic compounds have been identified but very few of them fit the required criteria of a potential drug. Fumagillin and particularly its synthetic analogue AGM 1470 might be developed for use in humans in the near future.

L6 ANSWER 34 OF 49 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 93071308 EMBASE
DOCUMENT NUMBER: 1993071308
TITLE: Epidermal growth factor stimulates vascular endothelial growth factor production by human malignant glioma cells: A model of glioblastoma multiforme pathophysiology.
AUTHOR: Goldman C.K.; Kim J.; Wong W.-L.; King V.; Brock T.; Gillespie G.Y.
CORPORATE SOURCE: Brain Tumor Research Laboratories, Department of Surgery, University of Alabama,Birmingham, AL 35294-0006, United States
SOURCE: Molecular Biology of the Cell, (1993) 4/1 (121-133). ISSN: 1059-1524 CODEN: MBCEEV
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Hypervascularity, focal necrosis, persistent cerebral edema, and rapid cellular proliferation are key histopathologic features of glioblastoma multiforme (GBM), the most common and malignant of human brain tumors. By immunoperoxidase and immunofluorescence, we definitively have demonstrated the presence of vascular endothelial growth factor (**VEGF**) and epidermal growth factor receptor (EGFr) in five out of five human glioma cell lines (U- 251MG, U-105MG, D-65MG, D-54MG, and CH-235MG) and in eight human GBM tumor surgical specimens. In vitro experiments with glioma cell lines revealed a consistent and reliable relation between EGFr activation and **VEGF** production; namely, EGF (1-20 ng/ml) stimulation of glioma cells resulted in a 25-125% increase in secretion of bioactive **VEGF**. Conditioned media (CM) prepared from EGF-stimulated glioma cell lines produced significant increases in cytosolic free intracellular concentrations of Ca2+ ([Ca2+](i)) in human umbilical vein endothelial cells (HUVECs). Neither EGF alone or CM from glioma cultures prepared in the absence of EGF induced [Ca2+](i) increases in HUVECs. Preincubation of glioma CM with A4.6.1, a monoclonal antibody to **VEGF**, completely abolished **VEGF**-mediated [Ca2+](i) transients in HUVECs. Likewise, induction by glioma-derived CM of von **Willebrand** factor release from HUVECs was completely blocked by A4.6.1 pretreatment. These observations provide a key link in understanding the basic cellular pathophysiology of GBM tumor angiogenesis, increased vascular permeability, and cellular proliferation. Specifically, EGF activation of EGFr expressed on glioma cells leads to enhanced secretion of **VEGF** by glioma cells. **VEGF** released by glioma cells in situ most likely accounts for pathognomonic histopathologic and clinical features of GBM tumors in patients, including striking tumor angiogenesis, increased cerebral edema and hypercoagulability manifesting as focal tumor necrosis, deep vein **thrombosis**, or pulmonary embolism.

L6 ANSWER 35 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2002:221488 BIOSIS
DOCUMENT NUMBER: PREV200200221488
TITLE: Analysis of intrapulmonary vessels and epithelial-endothelial interactions in the human developing lung.
AUTHOR(S): Maeda, Sumiko (1); Suzuki, Satoshi; Suzuki, Takashi; Endo, Mareyuki; Moriya, Takuya; Chida, Masayuki; Kondo, Takashi; Sasano, Hironobu
CORPORATE SOURCE: (1) Department of Thoracic Surgery, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryo-machi, Aoba-ku, Sendai, 980-8575: sumiko@idac.tohoku.ac.jp Japan
SOURCE: Laboratory Investigation, (March, 2002) Vol. 82, No. 3, pp. 293-301. http://labinvest.uscapjournals.org/. print. ISSN: 0023-6837.
DOCUMENT TYPE: Article
LANGUAGE: English

AB The establishment of a sufficiently wide and functional blood-gas interface is of critical importance in lung development, but development of the intrapulmonary vascular system including alveolar capillary vessels still remains unclear. In this study, we first characterized the structural development of the vascular system in accordance with that of airways in human fetal lungs at the pseudoglandular phase (8, 13, and 16 weeks gestation) by examining the immunohistochemical distribution of CD34 and alpha-smooth muscle actin (SMA). Using double immunohistochemistry and 3-dimensional reconstruction techniques, endothelial cells in the developing lung could be classified into two different types according to

the characteristics of their adjacent cells (presence or absence of SMA-positive cells) and their distribution (proximal or distal lung parenchyme). Endothelial cells without SMA-positive cells developed into a capillary network surrounding the budding components of distal airways during the mid-pseudoglandular phase before communicating with proximal vessels. We then examined the immunoreactivity of **thrombomodulin** and von **Willebrand** factor (vWF) in endothelial cells. Endothelial cells of the capillary network were mainly positive for vWF during the early gestational stages, but altered their phenotypes to those of mature lungs (vWF negative and **thrombomodulin** positive) during the terminal sac phase. We subsequently determined the immunohistochemical distribution of vascular endothelial growth factor (**VEGF**). Epithelial cells of the most distal airways were intensely positive for **VEGF**. These results suggest that **VEGF** present in airway epithelial cells is involved in the maturation as well as proliferation of capillary endothelial cells. Epithelial-endothelial interactions during lung development are considered very important in the establishment of the functional blood-gas interface.

L6 ANSWER 36 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:220599 BIOSIS
DOCUMENT NUMBER: PREV200200220599
TITLE: Ex vivo and in vivo primitive hematopoiesis from a non-hematopoietic stem cell.
AUTHOR(S): Reyes, Morayma (1); Koodie, Lisa; Jahagirdar, Balkrishna; Verfaillie, Catherine M.
CORPORATE SOURCE: (1) Stem Cell Institute, University of Minnesota, Minneapolis, MN USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 713a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Multipotent Adult Stem Cells (MASC) from, human bone marrow (BM) differentiate at the single cell level into neuroectodermal, endodermal and many mesodermal lineages, including endothelial cells. Because endothelium and blood are very closely related in ontogeny, we hypothesized that MASC can differentiate into hematopoietic cells. eGFP transduced human MASC, that are glycophorin-A (GlyA), CD45 and CD34 negative (n=20), were cocultured with the mouse yolk sac mesodermal cell line, YSM5, as suspension cell aggregates for 6 days in serum free medium supplemented with 10 ng/mL bFGF and **VEGF**. After six days, only eGFP+ cells (MASC progeny) remained and YSM5 cells had died. Remaining cells were transferred to methylcellulose cultures containing 10% fetal calf serum supplemented with 10 ng/mL BMP4, **VEGF**, bFGF, SCF, Flt3L, hyper IL6, TPO, and EPO for 2 weeks. In these cultures, we detected both adherent eGFP+ cells and small, round non-adherent cells, which formed many colonies attached to the adherent cells. The non-adherent and adherent fractions were collected separately and cultured in 10%FCS containing medium with 10 ng/mL **VEGF** and bFGF for 7 days. Adherent cells stained positive for vWF, formed vascular tubes when plated on ECM, and were able to uptake a-LDL, indicating their endothelial nature. 5-50% of the non-adherent cells stained positive for human specific GlyA and HLA-class I by flow cytometry. Gly-A+/HLA-class-I+ cells were selected by FACS. On Wright-Giemsa, these cells exhibited the characteristic morphology and staining pattern of primitive erythroblasts. Cells were benzidine+ and human Hb+ by immunoperoxidase. By RT-PCR these cells expressed human specific Hb-e, but not Hb-a. When replated in methylcellulose assay with 20%FCS and EPO, small erythroid colonies were seen after 10 days, and 100% of these colonies stained positive for human specific GlyA and Hb. As selection of MASC depends on the depletion of CD45 and Gly A+ cells from BM, and cultured MASC are CD45- and GlyA- at all times examined using both FACS and cDNA array analysis, contamination of MASC with hematopoietic cells is very unlikely. We have showed using PCR that the identical retroviral integration specific sequences was present in MASC differentiated to GlyA+ erythroblasts, endodermal, neuroectodermal endothelial and skeletal muscle cells, proving that a single MASC, which is of non-hematopoietic origin, differentiates into primitive erythroblasts, other mesodermal as well as neuroectodermal and endodermal cell types. When undifferentiated human MASC were transplanted into NOD/SCID mice, 0.5-5% of human GlyA+/HLA-class I+ were detected in BM and blood. In conclusion, we demonstrate here for the first time the ex vivo and in vivo differentiation of non-hematopoietic multipotent stem cells from adult human BM into primitive erythrocytes as well as other mesodermal, neuroectodermal and endodermal cell types.

L6 ANSWER 37 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:220257 BIOSIS
DOCUMENT NUMBER: PREV200200220257
TITLE: Bone marrow vascularization and **VEGF** levels in essential **thrombocythemia**.
AUTHOR(S): Vassallu, Patricia S. (1); Correa, Gabriel (1); Alvarez, Clarisa (1); Molinas, Pelisa (1)
CORPORATE SOURCE: (1) Hematologia Investigacion, Instituto de Investigaciones Medicas A. Lanari, Buenos Aires Argentina
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 630a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The aim of our study was to measure the levels of serum vascular endothelial growth factor (**VEGF**) and bone marrow vascularization in 42 patients with essential **thrombocythemia** (ET). **VEGF** was measured by ELISA technique (R&D Systems) in serum samples, 19 before treatment with anagrelide and 32 while on treatment. Vascular structures were immunostained for **VEGF**, CD31 and von **Willebrand** factor in 23 ET cases and 5 bone marrow samples from normal controls. Using light microscopy we counted the number of vessels per 500X high power field (HPF) in areas of most dense vascularization (hot spots), taking the average of ten randomly chosen areas for each antibody used. The serum levels of **VEGF** in ET patients were higher than those in normal controls (n:7), 688.9 pg/ml (4003.5-156) (median and range) vs 72.9 pg/ml (327-50), p=0.0001. When **VEGF** values were compared among patients who had samples before and during treatment no significant difference was found. Similar results were seen when the 19 patients before treatment with anagrelide were grouped into patients without any

treatment (n:10) and those who had received myelosuppression (n:9). By immunostaining ET bone marrow biopsy showed 4 (7.2-2.3) vesselsXHPF vs 1.8 (2.6-1.2) vesselsXHPF in normal controls, p=0.0017. No correlation was found when **VEGF** values were compared with the platelet levels, even when the patient population was grouped into those who had platelet counts higher than 600 000/mul and those who had lower values. No correlation was found when **VEGF** values were compared with hematocrit, leukocyte count, reticulin fibrosis or clinical manifestations. These results show an increased bone marrow angiogenic activity and **VEGF** overproduction in ET patients. Although platelets are an important source of **VEGF**, we found that raised **VEGF** levels are independent of platelet counts in our patients.

L6 ANSWER 38 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:151542 BIOSIS
DOCUMENT NUMBER: PREV200200151542
TITLE: Assessment of mild normobaric hypoxia on hemostatic and endothelial function.
AUTHOR(S): Hunt, Beverley J. (1); Hodkinson, Peter D.; Parmar, Kiran (1); Ernsting, John
CORPORATE SOURCE: (1) Haematology Department, GKT, London UK
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 2, pp. 54b. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 2 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Modern air travel entails a cabin altitude of between 1,520-2,440m (5000-8000ft) and thus exposure to mild hypoxia. The latter has been suggested as a risk factor for travellers **thrombosis**. Indeed, Bendz et al have suggested that a short period of hypobaric hypoxia causes activation of coagulation. We have tested the hypothesis that it is the hypoxia alone (i.e. without the change of environmental pressure seen in aeroplane cabins during flight) that causes activation of coagulation, possibly through endothelial cell activation (ECA). Local Ethical Committee approval was obtained. Six healthy male volunteers (age range 22-32), with no risk factors for venous **thrombosis** took part. They attended on two separate mornings starting between 9.00 and 10.00. They received a gas mixture through a well fitted silicone oronasal mask and a demand regulator from compressed gas cylinders (BOC Ltd., Guildford, UK) which contained either dry air (control) or a dry hypoxic gas mixture (12.8% O2 in N2, equivalent to breathing air at 3660m (12000ft) altitude) for three hours, during which time they were asked to remain seated and immobile. Validation by pulse oximetry, showed the subjects were appropriately hypoxic. Blood samples were taken before, immediately after and 24 hours after each run. Blood was taken from the antecubital fossa using uncuffed, flawless venepuncture and centrifuged at 2,000G and stored at minus 80degreeC. Full blood counts and plasma viscosity were performed at each time point. Soluble markers of ECA were measured using accepted ELISAs and included e-selectin, ICAM, VCAM, PAI-1, tissue factor, vWF and **VEGF**. Haemostatic markers included prothrombin fragment 1+2, p-selectin, D-dimers (all ELISA) and fibrinogen levels (Clauss). Statistical analysis was performed using the Mann-Whitney U-test. There was a significant increase in platelet ($p<0.04$) and white cell count, immediately post hypoxia compared to the control group, the latter was due to a neutrophilia ($p<0.04$), with a significant increase in plasma viscosity in both groups ($p<0.05$) at the same time. There was no significant change in PF 1+2, D-Dimer, p-selectin or **VEGF** levels. Markers of ECA including sol-ICAM & VCAM, showed no change in either group. An increase in fibrinogen levels was seen in both control and hypoxic groups immediately post, while vWF increased immediately post hypoxia ($p<0.04$), although this was not significantly different to post-control vWF. Significant falls in e-selectin ($p<0.003$) and PAI-1 ($p=0.002$) levels at 24 hours post were also seen in both groups. This small study suggests that activation of haemostasis or the endothelium is not associated with mild normobaric hypoxia. This is in contrast to the work of Bendz et al. Thus if the activation of coagulation reported by Bendz et al is to be believed, it supports the novel hypothesis that it is changes in environmental pressure rather than changes in oxygen partial pressure that are responsible for their findings. Alternatively, the findings of Bendz et al (which was an uncontrolled study) may not be real, as suggested by Bartsch et al. Further controlled studies are required to resolve whether changes in environmental pressure, or more prolonged periods of hypoxia, activate haemostasis.

L6 ANSWER 39 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:120090 BIOSIS
DOCUMENT NUMBER: PREV200200120090
TITLE: Aerosol delivery of PEI-p53 complexes inhibits B16-F10 lung metastases through regulation of angiogenesis.
AUTHOR(S): Gautam, Ajay; Densmore, Charles L.; Melton, Sara; Golunski, Eva; Waldrep, J. Clifford (1)
CORPORATE SOURCE: (1) Department of Molecular Physiology and Biophysics, Baylor College of Medicine, One Baylor Plaza, Houston, TX, 77030: jwaldrep@bcm.tmc.edu USA
SOURCE: Cancer Gene Therapy, (January, 2002) Vol. 9, No. 1, pp. 28-36. print.
ISSN: 0929-1903.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Inhibition of pulmonary metastases poses a difficult clinical challenge for current therapeutic regimens. We have developed an aerosol system utilizing a cationic polymer, polyethyleneimine (PEI), for topical gene delivery to the lungs as a novel approach for treatment of lung cancer. Using a B16-F10 murine melanoma model in C57BL/6 mice, we previously demonstrated that aerosol delivery of PEI-p53 DNA resulted in highly significant reductions in the tumor burden ($P < .001$) in treated animals, and also lead to about 50% increase in the mean length of survival of the mice-bearing B16-F10 lung tumors. The mechanisms of this antitumor effect of p53 are investigated in this report. Here, we demonstrate that the p53 transfection leads to an up-regulation of the antiangiogenic factor **thrombospondin**-1 (TSP-1) in the lung tissue and the serum of the mice. Furthermore, there is a down-regulation of vascular endothelial growth factor (**VEGF**) in the lung tissue and serum of the B16-F10 tumor-bearing mice treated with PEI-p53 DNA complexes, compared with untreated tumor-bearing animals. In addition, staining for von **Willebrand** factor (vWF), a marker for the angiogenic blood vessels, revealed that p53 treatment leads to a decrease in the angiogenic phenotype of the B16-F10 tumors. Immunohistochemistry for transgene expression reveals that the PEI-p53 aerosol complexes transfect mainly the

epithelial cells lining the airways, with diffuse transfection in the alveolar lining cells, as well as, the tumor foci in the lung tissue. There was also some evidence of apoptosis in the lung tumor foci of animals treated with p53. The data suggest that aerosol delivery of PEI-p53 complexes leads to inhibition of B16-F10 lung metastases, in part by suppression of angiogenesis.

L6 ANSWER 40 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:545321 BIOSIS
DOCUMENT NUMBER: PREV200100545321
TITLE: Angiogenesis and phenotypic alteration of alveolar capillary endothelium in areas of neoplastic cell spread in primary lung adenocarcinoma.
AUTHOR(S): Jin, Enjing; Ghazizadeh, Mohammad; Fujiwara, Masakazu; Nagashima, Mikio; Shimizu, Hajime; Ohaki, Yoshiharu; Arai, Satoru; Gomibuchi, Makoto; Takemura, Tamiko; Kawanami, Oichi (1)
CORPORATE SOURCE: (1) Department of Molecular Pathology, Institute of Gerontology, Nippon Medical School, 1-396 Kosugi-cho, Nakahara-ku Kawasaki-shi, Kanagawa-ken, 211-8533: kawanami/ig@nms.ac.jp Japan
SOURCE: Pathology International, (September, 2001) Vol. 51, No. 9, pp. 691-700. print.
ISSN: 1320-5463.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Normal alveolar capillary endothelium is quiescent in nature and displays anticoagulant **thrombomodulin** (TM) on its surface. The cytoplasms of these endothelial cells are ultrastructurally non-fenestrated type, and they barely express von **Willebrand** factor (vWf). Alveolar fibrosis is accompanied by a capillary endothelium reactive for vWf, and a loss of TM expression. In primary lung adenocarcinoma, neovascularization occurs in association with alveolar fibrosis. In order to study basic factors related to angiogenesis and phenotypic changes of the capillaries located in tumor-bearing alveolar walls, we examined 37 primary lung adenocarcinomas with electron microscopy and confocal laser scanning microscopy with antibodies for TM, vWf, vascular endothelial growth factor (**VEGF**), and its receptors (KDR and Flt-1), and proliferating markers (Ki-67/proliferating cell nuclear antigen). Tissues microdissected specifically from alveolar walls were used for reverse transcription-polymerase chain reaction (RT-PCR) to assess expressions of mRNA isoforms of **VEGF** and its receptors. New capillary branching was found by ultrastructural study in the alveolar walls in 12% of the patients. Nuclei of the capillary endothelial cells were reactive for proliferating cell markers. Endothelial fenestrae were developed in 65% of the patients, TM reactivity was lost in the alveolar capillaries, and their cell cytoplasms obtained a reactivity for vWf through a transitional mosaic-like distribution pattern of both antigens. Besides cytoplasmic **VEGF** expression in neoplastic cells, tumor-bearing alveolar walls showed significant expression of mRNA of **VEGF165** and KDR. These findings imply that angiogenesis and phenotypic changes of the alveolar capillaries are closely related to a higher expression of tumor-associated **VEGF165** and of KDR in the alveolar walls in primary lung adenocarcinoma.

L6 ANSWER 41 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:431334 BIOSIS
DOCUMENT NUMBER: PREV200100431334
TITLE: Systemic endothelial cell markers in primary antiphospholipid syndrome.
AUTHOR(S): Williams, Frances M. K.; Parmar, Kiran; Hughes, Graham R. V.; Hunt, Beverley J. (1)
CORPORATE SOURCE: (1) Department of Haematology, St Thomas' Hospital, Lambeth Palace Road, 4th Floor North Wing, London, SE1 7EH: Beverley.hunt@gstt.sthames.nhs.uk UK
SOURCE: Thrombosis and Haemostasis, (November, 2000) Vol. 84, No. 5, pp. 742-746. print.
ISSN: 0340-6245.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The pathogenic mechanism underlying the prothrombotic tendency of Hughes' or antiphospholipid syndrome (APS) has not been elucidated. Numerous procoagulant mechanisms have been tested including platelet activation, monocyte tissue factor (TF) expression and endothelial cell (EC) activation. There is some evidence for the latter from studies on cultured human umbilical vein endothelial cells (HUVEC). Incubation with antiphospholipid antibodies (aPL) induces EC activation in vitro. We investigated whether there was evidence of EC perturbation in vivo using enzyme-linked immunosorbant assays (ELISAs) for soluble markers of EC dysfunction. Serum and plasma were collected from controls and patients with primary APS and ELISAs performed to quantify soluble vascular cell adhesion molecule (sVCAM), soluble intercellular adhesion molecule-1 (sICAM-1), interleukin-6 (IL-6), endothelin-1 (ET-1), von **Willebrand** factor (vWF) and soluble tissue factor (sTF). In addition, soluble p-selectin (p-selectin) and vascular endothelial growth factor (**VEGF**) were measured: the former as a marker of platelet activation, the latter as a potential mediator of TF expression. No significant differences in the levels of blood-borne soluble markers were detected between the patient and control groups except for **VEGF** and sTF, patients having significantly higher levels of **VEGF** and sTF than controls ($p<0.05$). These results suggest plasma soluble tissue factor and **VEGF** may play a role in the pathogenesis of **thrombosis** in APS, although the cell of origin of these molecules remains unclear.

L6 ANSWER 42 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:203094 BIOSIS
DOCUMENT NUMBER: PREV200100203094
TITLE: Age-related macular degeneration is associated with increased vascular endothelial growth factor, hemorheology and endothelial dysfunction.
AUTHOR(S): Lip, Peck-Lin; Blann, Andrew D.; Hope-Ross, Monique; Gibson, Jonathan M.; Lip, Gregory Y. H. (1)
CORPORATE SOURCE: (1) University Department of Medicine, City Hospital, Birmingham, B18 7QH UK
SOURCE: Ophthalmology, (April, 2001) Vol. 108, No. 4, pp. 705-710. print.
ISSN: 0161-6420.
DOCUMENT TYPE: Article
LANGUAGE: English

SUMMARY LANGUAGE: English

AB Objective: To investigate laboratory evidence of abnormal angiogenesis, hemorheologic factors, endothelial damage/dysfunction, and age-related macular degeneration (ARMD). Design: Comparative cross-sectional study. Participants: We studied 78 subjects (26 men and 52 women; mean age 74 years; standard deviation (SD) 9.0) with ARMD attending a specialist referral clinic. Subjects were compared with 25 healthy controls (mean age, 71 years; SD, 11). Intervention and Outcome Measures: Levels of vascular endothelial growth factor (**VEGF**, an index of angiogenesis), hemorheologic factors (plasma viscosity, hematocrit, white cell count, hemoglobin, platelets), fibrinogen (an index of rheology and hemostasis), and von **Willebrand** factor (a marker of endothelial dysfunction) were measured. Results: Median plasma **VEGF** (225 vs. 195 pg/ml, P = 0.019) and mean von **Willebrand** factor (124 vs. 99 IU/dl, P = 0.0004) were greater in ARMD subjects than the controls. Mean plasma fibrinogen and plasma viscosity levels were also higher in the subjects (both P < 0.0001). There were no significant differences in other indices between cases and controls. When "dry" (drusen, atrophy, n = 28) and "exudative" (n = 50) ARMD subjects were compared, there was no significant differences in **VEGF**, fibrinogen, viscosity, or von **Willebrand** factor levels. There were no significant correlations between the measured parameters. Stepwise multiple regression analysis did not demonstrate any significant clinical predictors (age, gender, smoking, body mass index, history of vascular disease, or hypertension) for plasma **VEGF** or fibrinogen levels, although smoking status was a predictor of plasma von **Willebrand** factor levels (P < 0.05). Conclusions: This study suggests an association between markers of angiogenesis (**VEGF**), hemorheologic factors, hemostasis, endothelial dysfunction, and ARMD. The interaction between abnormal angiogenesis and the components of Virchow's triad for **thrombogenesis** may in part contribute to the pathogenesis of ARMD.

L6 ANSWER 43 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:100666 BIOSIS
DOCUMENT NUMBER: PREV200100100666
TITLE: Neoplastic invasion of primary adeno-carcinoma induces phenotypic alteration to alveolar capillary endothelium in the lung.
AUTHOR(S): Kawanami, O. (1); Jin, E. (1); Ghazizadeh, M. (1); Fujiwara, M. (1); Jiang, L. (1); Shimizu, H. (1); Arai, S. (1); Ohaki, Y. (1)
CORPORATE SOURCE: (1) Department of Molecular Pathology, Institute of Gerontology and Hokusoh Hospital, Nippon Medical School, Kawasaki Japan
SOURCE: Journal of Submicroscopic Cytology and Pathology, (July, 2000) Vol. 32, No. 3, pp. 363. print.
Meeting Info.: XIth International Vascular Biology Meeting Geneva, Switzerland September 05-09, 2000
ISSN: 1122-9497.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L6 ANSWER 44 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:361286 BIOSIS
DOCUMENT NUMBER: PREV200000361286
TITLE: Endothelial-like cells derived from human CD14 positive monocytes.
AUTHOR(S): Pujol, Beatriz Fernandez; Lucibello, Frances C.; Gehling, Ursula M.; Lindemann, Katharina; Weidner, Natalja; Zuzarte, Mary-Lou; Adamkiewicz, Juergen; Elsaesser, Hans-Peter; Mueller, Rolf; Havemann, Klaus (1)
CORPORATE SOURCE: (1) Institute for Molecular Biology and Tumor Research (IMT), Philipps-University, Emil-Mannkopff-Strasse 2, D-35033, Marburg Germany
SOURCE: Differentiation, (May, 2000) Vol. 65, No. 5, pp. 287-300. print.
ISSN: 0301-4681.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In the present study, we show that endothelial-like cells (ELCs) can develop from human CD14-positive mononuclear cells (CD14 cells) in the presence of angiogenic growth factors. The CD14 cells became loosely adherent within 24 h of culture and subsequently underwent a distinct process of morphological transformation to caudated or oval cells with eccentric nuclei. After 1 week in culture the cells showed a clear expression of endothelial cell markers, including von **Willebrand** factor (vWF), CD144 (VE-cadherin), CD105 (endoglin), acetylated low-density lipoprotein (AC-LDL)-receptor, CD36 (**thrombospondin** receptor), FLT-1, which is vascular endothelial cell growth factor (**VEGF**) receptor-1, and, to a weaker extent, KDR (**VEGF** receptor-2). Furthermore, in these cells structures resembling Weibel-Palade bodies at different storage stages were identified by electron microscopy, and upon culturing on three-dimensional fibrin gels the cells build network-like structures. In addition, cell proliferation and vWF expression was stimulated by **VEGF**, and the endothelial cell adhesion molecules CD54 (ICAM-1), and CD106 (VCAM-1) became transiently inducible by tumor necrosis factor-alpha (TNF-alpha). In contrast, the dendritic markers CD1a, and CD83 were not expressed to any significant extent. The expression of CD68, CD80 (B7-1), CD86 (B7-2), HLA-DR and CD36 may also suggest that ELCs might be related to macrophages, sinus lining or microvascular endothelial cells. Taken together, our observations indicate that ELCs can differentiate from cells of the monocytic lineage, suggesting a closer relationship between the monocyte/macrophage- and the endothelial cell systems than previously supposed.

L6 ANSWER 45 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:379992 BIOSIS
DOCUMENT NUMBER: PREV199900379992
TITLE: The influence of LDL-apheresis on changes in atherogenic lipid profile, endothelial function (NOx, vWF, **VEGF165**) and exercise tolerance in severe CAD patients.
AUTHOR(S): Dembinska-Kiec, A. (1); Bartus, S.; Konduracka, E.; Partyka, L.; Leszczynska-Golabek, I.; Zdzienicka, A.; Hartwich, J.; Guevara, I.; Pankiewicz, J.; Dudek, D.; Piwowarska, W.; Dubiel, J. S.; Dziatkowiak, A.
CORPORATE SOURCE: (1) Dpt. of Clinical Biochemistry, Coronary Artery Disease Clinic, Jagiellonian University School of Medicine, Krakow Poland

SOURCE: European Journal of Clinical Investigation, (April, 1999) Vol. 29, No. SUPPL. 1, pp. 76. Meeting Info.: 33rd Meeting of the European Society for Clinical Investigation Milan, Italy April 8-10, 1999 European Society for Clinical Investigation . ISSN: 0014-2972.
DOCUMENT TYPE: Conference
LANGUAGE: English

L6 ANSWER 46 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:282685 BIOSIS
DOCUMENT NUMBER: PREV199800282685
TITLE: The influence of LDL-apheresis on **VEGF165**, Von **Willebrand** factor and beta-TG levels in resistant hypercholesterolemia.
AUTHOR(S): Bartus, S. (1); Konduracka, E.; Partyka, L. (1); Lesaczynska-Golabek, I. (1); Zdienicka, A. (1); Guevara, I. (1); Pankiewicz, J. (1); Dudek, D.; Piwowarska, W.; Dubiel, J. S.; Dziatkowiak, A.; Dembinska-Kiec, A.; Sinzinger, H.
CORPORATE SOURCE: (1) Dep. Clin. Biochem., Jagiellonian Univ., Cracow Poland
SOURCE: European Journal of Clinical Investigation, (May, 1998) Vol. 28, No. SUPPL. 1, pp. A55. Meeting Info.: 32nd Annual Scientific Meeting of the European Society for Clinical Investigation Cracow, Poland April 16-19, 1998 European Society for Clinical Investigation . ISSN: 0014-2972.
DOCUMENT TYPE: Conference
LANGUAGE: English

L6 ANSWER 47 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:95753 BIOSIS
DOCUMENT NUMBER: PREV199800095753
TITLE: Why do immature hemangiomas regress.
AUTHOR(S): Eeckhout, I. (1); Leaute-Labreze, C.; Taieb, A.
CORPORATE SOURCE: (1) Serv. Dermatol., Hop. Univ., De Pintelaan 185, B-9000 Gent Belgium
SOURCE: Annales de Dermatologie et de Venereologie, (Nov., 1997) Vol. 124, No. 11, pp. 800-804. ISSN: 0151-9638.
DOCUMENT TYPE: Article
LANGUAGE: French

L6 ANSWER 48 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:353181 BIOSIS
DOCUMENT NUMBER: PREV199598367481
TITLE: Human chorionic gonadotropin-dependent expression of vascular endothelial growth factor/vascular permeability factor in human granulosa cells: Importance in ovarian hyperstimulation syndrome.
AUTHOR(S): Neulen, Joseph (1); Yan, Zhaoping; Raczek, Sonja; Weindel, Karin; Keck, Christoph; Weich, Herbert A.; Marme, Dieter; Breckwoldt, Meinert
CORPORATE SOURCE: (1) Dep. Obstetrics Gynecol., Univ. Freiburg, Hugstetter Strasse 55, 79106 Freiburg Germany
SOURCE: Journal of Clinical Endocrinology & Metabolism, (1995) Vol. 80, No. 6, pp. 1967-1971. ISSN: 0021-972X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Ovarian hyperstimulation syndrome (OHSS) is a severe complication arising from controlled ovarian stimulation treatment. This iatrogenic condition is potentially lethal and occurs in 0.3-5% of stimulated ovarian cycles. hCG exacerbates OHSS. The pathophysiology of OHSS is still unknown; therefore, treatment regimens are aimed at ameliorating symptoms. Prominent features of OHSS are an elevated risk of **thromboembolism** due to enhanced production of von **Willebrand** factor by endothelial cells and ascites, or pulmonary edema due to increased vascular permeability followed by third space fluid accumulation. Both of these sequelae can be evoked by vascular endothelial growth factor (**VEGF**), also known as vascular permeability factor (VPF). High concentrations of **VEGF**/VPF have been demonstrated in ascitic fluid from patients with OHSS, but the source of **VEGF**/VPF in these patients remained unidentified. Here we report that the messenger ribonucleic acid expression of **VEGF**/VPF in human luteinized granulosa cells (GCs) is dose and time dependently enhanced by hCG in vitro. Furthermore, **VEGF**/VPF proteins are produced by GCs. Our results suggest that the effects of hCG on the development and course of OHSS may be mediated by the production of **VEGF**/VPF by GCs.

L6 ANSWER 49 OF 49 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1993:230726 BIOSIS
DOCUMENT NUMBER: PREV199395121901
TITLE: Epidermal growth factor stimulates vascular endothelial growth factor production by human malignant glioma cells: A model of glioblastoma multiforme pathophysiology.
AUTHOR(S): Goldman, Corey K. (1); Kim, Jin; Wong, Wai-Lee; King, Vickie; Brock, Tommy; Gillespie, G. Yancey (1)
CORPORATE SOURCE: (1) Brain Tumor Res. Lab., Div. Neurosurg., Dep. Surg., Univ. Ala. Birmingham, Birmingham, AL 35294-0006
SOURCE: Molecular Biology of the Cell, (1993) Vol. 4, No. 1, pp. 121-133. ISSN: 1059-1524.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Hypervascularity, focal necrosis, persistent cerebral edema, and rapid cellular proliferation are key histopathologic features of glioblastoma multiforme (GBM), the most common and malignant of human brain tumors. By immunoperoxidase and immunofluorescence, we definitively have demonstrated the presence of vascular endothelial growth factor (**VEGF**) and epidermal growth factor receptor (EGFr) in five out of five human glioma cell lines (U-251MG, U-105MG, D-65MG, D-54MG, and CH-235MG) and in eight human GBM tumor surgical specimens. In vitro experiments with glioma cell lines revealed a consistent and reliable relation between EGFr activation and **VEGF** production; namely, EGF (1-20 ng/ml) stimulation of glioma cells resulted in a 25-125% increase in secretion of bioactive **VEGF**. Conditioned media (CM) prepared from EGF-stimulated glioma cell lines produced significant increases in cytosolic free intracellular concentrations of Ca-2+ ((Ca-2+)-i) in human umbilical vein endothelial cells (HUVECs). Neither EGF alone or CM from glioma cultures prepared in the absence of EGF induced (Ca-2+)-i increases in HUVECs. Preincubation of glioma CM with A4.6.1, a monoclonal antibody to **VEGF**, completely

abolished **VEGF**-mediated (Ca-2+)-i transients in HUVECs. Likewise, induction by glioma-derived CM of von **Willebrand** factor release from HUVECs was completely blocked by A4.6.1 pretreatment. These observations provide a key link in understanding the basic cellular pathophysiology of GBM tumor angiogenesis, increased vascular permeability, and cellular proliferation. Specifically, EGF activation of EGFr expressed on glioma cells leads to enhanced secretion of **VEGF** by glioma cells. **VEGF** released by glioma cells in situ most likely accounts for pathognomonic histopathologic and clinical features of GBM tumors in patients, including striking tumor angiogenesis, increased cerebral edema and hypercoagulability manifesting as focal tumor necrosis, deep vein **thrombosis**, or pulmonary embolism.

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=> s stewart M?/au or person R?/au or Noujaim A?/au
L9        6154 STEWART M?/AU OR PERSON R?/AU OR NOUJAIM A?/AU

=> s l9 and (vWF or Willebrand?)
L10         60 L9 AND (VWF OR WILLEBRAND?)

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11          28 DUP REM L10 (32 DUPLICATES REMOVED)

=> dis l11 1-28 ibib abs

L11  ANSWER 1 OF 28     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:   2002226366     IN-PROCESS
DOCUMENT NUMBER:    21957392   PubMed ID: 11958804
TITLE:              Assessment of omega-fatty-acid-supplemented human platelets
                    for potential improvement in long-term storage.
AUTHOR:             Krishnamurti Chitra; Stewart Michael W; Cutting
                    Mary A; Rothwell Stephen W
CORPORATE SOURCE:   Department of Blood Research, Walter Reed Army Institute of
                    Research, Silver Spring, MD 20910-7500, USA..
                    krishnac@nhlbi.nih.gov
SOURCE:             THROMBOSIS RESEARCH, (2002 Jan 15) 105 (2) 139-45.
                    Journal code: 0326377. ISSN: 0049-3848.
PUB. COUNTRY:       United States
                    Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE:         Entered STN: 20020420
                    Last Updated on STN: 20020420
AB   Uptake of omega (omega)-3 fatty acids can influence membrane stability and
     cell mobility. We investigated the effects of omega-3 and -6 fatty acids
     on the hemostatic efficacy of human platelets using an in vivo rabbit
     bleeding model. In vitro assays such as platelet aggregation, vWF
     bead-mediated ATP release and platelet adhesion to beads (measured by the
     residual platelet count [RPC] [free platelet count after reacting with the
     beads]/[baseline platelet count]x 100=%RPC; a high %RPC indicates reduced
     platelet function) were conducted on platelets treated with 1% fish oil
     (omega-3); 2% fish oil emulsion or 1% soy oil (omega-6). Oil treatment of
     platelets reduced the vWF bead-induced ATP release
     insignificantly. Addition of omega-3 agents reduced physical reactivity
     (%RPC) with the vWF beads by a factor of 1.2 (oil) and 1.9
     (emulsion). The omega-6 oil enhanced reactivity by a factor of 1.7. After
     washing to remove excess reagent, platelet resuspension was most efficient
     with the omega-3 emulsion. Platelet function was higher with the
     omega-3-treated platelets (%RPC=52.3%, omega-3 oil; 63.3%, omega-3
     emulsion vs. 85%, omega-6 oil; 82% untreated platelets).
     Ethyl-palmitate-treated thrombocytopenic rabbits were infused with human
     platelets. Survival times of the treated platelets, as monitored by flow
     cytometry (6.2-8.2 h) were comparable to untreated platelets (8.6 h). In
     the rabbit kidney injury model, blood loss after infusion of the treated
     platelets was similar to that of saline-infused rabbits (75.3+/-3.4 g).
     However, platelets washed prior to infusion reduced blood loss to a value
     comparable to that of fresh platelets (48.3+/-5 g). Furthermore, the
     presence of the infused platelets at the injury site was clearly
     visualized using FITC-tagged anti CD42a antibody. Thus, the omega-3-based
     agents protect the platelets from damage during the washing procedure as
     demonstrated in vitro by improved platelet resuspension, low %RPC, high
     stimulus-responsive ATP secretion and a reduction in blood loss in vivo.

L11  ANSWER 2 OF 28     MEDLINE                          DUPLICATE 2
ACCESSION NUMBER:   2001668052     MEDLINE
DOCUMENT NUMBER:    21538488   PubMed ID: 11682459
TITLE:              Role of von Willebrand factor in tumour
                    cell-induced platelet aggregation: differential regulation
                    by NO and prostacyclin.
AUTHOR:             Jurasz P; Stewart M W; Radomski A; Khadour F;
                    Duszyk M; Radomski M W
CORPORATE SOURCE:   Department of Pharmacology, University of Alberta,
                    Edmonton, Alberta, T6G 2H7, Canada.
SOURCE:             BRITISH JOURNAL OF PHARMACOLOGY, (2001 Nov) 134 (5)
                    1104-12.
                    Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY:       England: United Kingdom
                    Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200112
ENTRY DATE:         Entered STN: 20011121
                    Last Updated on STN: 20020123
                    Entered Medline: 20011207
AB   1. We have studied the effects of a novel agonist, solid-phase von
     Willebrand Factor (sVWF), on tumour cell-induced platelet
     aggregation (TCIPA). 2. Washed platelet suspensions were obtained from
     human blood and the effects of HT-1080 human fibrosarcoma cells and sVWF
     on platelets were studied using aggregometry, phase-contrast microscopy,
     and flow cytometry. 3. Incubation of platelets with sVWF (1.2 microg
     ml(-1)) and HT-1080 cells (5 x 10(3) ml(-1)) resulted in a two-phased
     reaction characterized first by the adhesion of platelets to sVWF, then by
     aggregation. 4. TCIPA in the presence of sVWF was inhibited by
     S-nitroso-glutathione (GSNO, 100 microM) and prostacyclin (PGI(2), 30 nM).
     5. Platelet activation in the presence of tumour cells and sVWF resulted
     in the decreased surface expression of platelet glycoprotein (GP)Ib and
     up-regulation of GPIIb/IIIa receptors. 6. Pre-incubation of platelets with
     PGI(2) (30 nM) resulted in inhibition of sVWF-tumour cell-stimulated
     platelet surface expression of GPIIb/IIIa as measured by flow cytometry
     using antibodies directed against both non-activated and activated
     receptor. In contrast, GSNO (100 microM) did not affect sVWF-tumour
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cell-stimulated platelet surface expression of GPIIb/IIIa. 7. Flow cytometry performed with PAC-1 antibodies that bind only to the activated GPIIb/IIIa revealed that GSNO (100 microM) caused inhibition of activation of GPIIb/IIIa. 8. The inhibitors exerted no significant effects on TCIPA-mediated changes in GPIb. 9. Thus, sVWF potentiates the platelet-aggregatory activity of HT-1080 cells and these effects appear to be mediated via up-regulation of platelet GPIIb/IIIa. 10. Prostacyclin and NO inhibit TCIPA-sVWF-mediated platelet aggregation. The mechanisms of inhibition of this aggregation by PGI(2) differ from those of NO.

L11 ANSWER 3 OF 28 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001668047 MEDLINE
DOCUMENT NUMBER: 21538478 PubMed ID: 11682449
TITLE: Pharmacological characteristics of solid-phase von **Willebrand** factor in human platelets.
AUTHOR: Radomski A; **Stewart M W**; Jurasz P; Radomski M W
CORPORATE SOURCE: Department of Pharmacology, University of Alberta, Edmonton, Alberta, T6G 2H7 Canada.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (2001 Nov) 134 (5) 1013-20.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011121
Last Updated on STN: 20020123
Entered Medline: 20011207

AB 1. The pharmacological characteristics of solid-phase von **Willebrand** factor (svWF), a novel platelet agonist, were studied. 2. Washed platelet suspensions were obtained from human blood and the effects of svWF on platelets were measured using aggregometry, phase-contrast microscopy, flow cytometry and zymography. 3. Incubation of platelets with svWF (0.2 - 1.2 microg ml(-1)) resulted in their adhesion to the ligand, while co-incubations of svWF with subthreshold concentrations of ADP, collagen and thrombin resulted in aggregation. 4. 6B4 inhibitory anti-glycoprotein (GP)Ib antibodies abolished platelet adhesion stimulated by svWF, while aggregation was reduced in the presence of 6B4 and N-Acetyl-Pen-Arg-Gly-Asp-Cys, an antagonist of GPIIb/IIIa. 5. Platelet adhesion stimulated with svWF was associated with a concentration-dependent increase in expression of GPIb, but not of GPIIb/IIIa. 6. In contrast, collagen (0.5 - 10.0 microg ml(-1)) caused down-regulation of GPIb and up-regulation of GPIIb/IIIa in platelets. 7. Solid-phase **vWF** (1.2 microg ml(-1)) resulted in the release of MMP-2 from platelets. 8. Inhibition of MMP-2 with phenanthroline (10 microM), but not with aspirin or apyrase, inhibited platelet adhesion stimulated with svWF. 9. In contrast, human recombinant MMP-2 potentiated both the effects of svWF on adhesion and up-regulation of GPIb. 10. Platelet adhesion and aggregation stimulated with svWF were reduced by S-nitroso-n-acetyl-penicillamine, an NO donor, and prostacyclin. 11. Thus, stimulation of human platelets with svWF leads to adhesion and aggregation that are mediated via activation of GPIb and GPIIb/IIIa, respectively. 12. Mechanisms of activation of GPIb by svWF involve the release of MMP-2, and are regulated by NO and prostacyclin.

L11 ANSWER 4 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:322391 BIOSIS
DOCUMENT NUMBER: PREV200100322391
TITLE: Treatment of platelets with fatty acids stabilizes platelet function in vitro and in vivo.
AUTHOR(S): Krishnamurti, Chitra (1); **Stewart, Michael W.**; Cutting, Mary A. (1); Rothwell, Stephen W. (1)
CORPORATE SOURCE: (1) Walter Reed Army Institute of Research, Silver Spring, MD USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 658a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Uptake of omega-3 fatty acids can influence membrane stability, fluidity and cell mobility. We have investigated the effects of omega-3 and -6 fatty acids on the hemostatic efficacy of human platelets. Human platelet rich plasma was incubated with either 1% fish oil (omega-3) or 2% fish oil emulsion or 1% soy oil (omega-6) for 30 min at 22degreeC. In vitro platelet function studies included platelet aggregation, **vWF** bead mediated ATP release and platelet adhesion to beads measuring the percentage residual platelet count (% RPC; a high %RPC equates to a reduced platelet function). The addition of omega-3 based agents reduced the **vWF** bead-induced ATP release by 10%, while the omega-6 based agent had no effect on the ATP release. In addition, the omega-3 based agents reduced the % RPC by a factor of 1.2 and 1.9 for the emulsion, while the omega-6 based oil enhanced the %RPC by 1.7. Recovery of platelets, after washing with buffer to remove excess reagent, was most efficient with the omega-3 emulsion (38% for treated vs 29% for control). In addition, platelet function after washing was better maintained with the omega-3 treated platelets (% RPC= 52.3% for the omega-3 oil, 63.3% for the omega-3 emulsion vs 85% for the omega-6 oil, which was similar to untreated platelets 82%). In our in vivo model, rabbits were made thrombocytopenic with busulfan and treated with ethyl palmitate (EP) one day prior to infusion of human platelets. Platelets survival was monitored by flow cytometry using anti CD42a (a selective marker for human platelets). Data showed that the survival times of human platelets treated with 1% omega-3 oil (6.2 h), 2% omega-3 emulsion (7 h) and 1% omega-6 oil (8.2 h) was comparable to the survival of fresh untreated platelets (8.6 h). In EP-treated thrombocytopenic rabbits, blood loss was assessed in a kidney surgery model. Blood loss in rabbits infused with oil-treated platelets was 76.3 +- 8.2 g (omega-3), 82.3 +- 7.5 g (omega-3 emulsion), and 70.3 +- 5.4 g (omega-6). This was similar to blood loss in saline infused rabbits (75.3 +- 3.4 g). However, when oil-treated platelets were washed prior to infusion, blood loss was reduced to 42.4 +- 7.1g (omega-3 oil), 39.1 +- 7.2 g (omega-3 emulsion) and 42.9 +- 2.5 g (omega-6 oil). This was comparable to the blood loss in rabbits infused with fresh platelets (48.3 +- 5 g). Thus, the data indicate that the omega-3 based agents protect the platelets from damage during the washing procedure as demonstrated in vitro by improved platelet recovery, low % RPC, high stimulus-responsive ATP secretion and a reduction in blood loss in vivo.

L11 ANSWER 5 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:122674 BIOSIS
DOCUMENT NUMBER: PREV199900122674
TITLE: Evaluation of ANTI-IIb/IIIa IC50 in platelet hypo- and hyper-responsive patient populations using a novel platelet function assay.
AUTHOR(S): **Stewart, M. W.** (1); Etches, W. S.; Larratt, L.; Dzavik, V.; Mousa, S.
CORPORATE SOURCE: (1) Thrombotics Inc., Edmonton, AB Canada
SOURCE: Blood, (Nov. 15, 1998) Vol. 92, No. 10 SUPPL. 1 PART 1-2, pp. 74B.
Meeting Info.: 40th Annual Meeting of the American Society of Hematology Miami Beach, Florida, USA December 4-8, 1998 The American Society of Heamatology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L11 ANSWER 6 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:122663 BIOSIS
DOCUMENT NUMBER: PREV199900122663
TITLE: Adhesion of human platelets to **VWF**-mediated dense granular secretion is a platelet alphaIIbbeta3 integrin-dependent process.
AUTHOR(S): Mousa, Shaker A. (1); Lorelli, William; Forsythe, Mark; **Stewart, M. W.**
CORPORATE SOURCE: (1) DuPont Pharmaceuticals Co., Wilmington, DE USA
SOURCE: Blood, (Nov. 15, 1998) Vol. 92, No. 10 SUPPL. 1 PART 1-2, pp. 71B.
Meeting Info.: 40th Annual Meeting of the American Society of Hematology Miami Beach, Florida, USA December 4-8, 1998 The American Society of Heamatology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L11 ANSWER 7 OF 28 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 97306128 MEDLINE
DOCUMENT NUMBER: 97306128 PubMed ID: 9163596
TITLE: Platelet activation by a novel solid-phase agonist: effects of **VWF** immobilized on polystyrene beads.
AUTHOR: **Stewart M W**; Etches W S; Boshkov L K; Mant M J; Gordon P A; Shaw A R
CORPORATE SOURCE: Department of Laboratory Medicine and Pathology, University of Alberta Hospitals, Edmonton, Canada.
SOURCE: BRITISH JOURNAL OF HAEMATOLOGY, (1997 May) 97 (2) 321-9.
Journal code: AXC; 0372544. ISSN: 0007-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 19970630
Entered Medline: 19970619

AB The interaction between platelets stirred in suspension and **VWF** immobilized on polystyrene beads was studied. Platelets aggregated and released ATP in response to stirring with **VWF** beads. Closer examination of the interaction using transmission electron microscopy revealed that the platelets did not simply aggregate with one another but initially adhered to the beads and spread. Platelets in suspension then bound to the bead-adherent platelets forming layers of platelets associated with each bead. The **VWF** bead-induced platelet activation was completely inhibited by addition of monoclonal antibody (mAb) to GPIb or GPIIb/IIIa. In addition, the activation response was inhibited in the presence of aspirin, indomethacin or the thromboxane receptor antagonist BM13.177, demonstrating a dependence on an intact cyclo-oxygenase pathway. Platelet function studies were carried out on 30 patients with a history of mild bleeding using conventional optical aggregation and **VWF** bead-induced platelet activation. 12 patients were abnormal by conventional optical aggregometry, whereas 27 patients showed depressed ATP release in response to **VWF** beads. The results suggest that easily-bruised patients may have a platelet function defect rather than a vascular-based abnormality and that **VWF** bead-induced platelet activation is a more sensitive test for detecting platelet dysfunction.

L11 ANSWER 8 OF 28 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 97158590 MEDLINE
DOCUMENT NUMBER: 97158590 PubMed ID: 9005950
TITLE: **vWf** inhibitor detection by competitive ELISA.
AUTHOR: **Stewart M W**; Etches W S; Shaw A R; Gordon P A
CORPORATE SOURCE: Department of Laboratory Medicine and Pathology, University of Alberta Hospitals, Edmonton, Canada.
SOURCE: JOURNAL OF IMMUNOLOGICAL METHODS, (1997 Jan 15) 200 (1-2) 113-9.
Journal code: IFE; 1305440. ISSN: 0022-1759.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970227
Last Updated on STN: 19970227
Entered Medline: 19970213

AB An inhibitor to von **Willebrand** factor (**vWf**) was detected in the plasma from two patients with histories of mild bleeding and one patient with a severe deficiency in the Factor VIII complex using a competitive enzyme-linked immunosorbent assay (ELISA) procedure. IgG antibodies from the patients' plasmas were shown to bind to **vWf** immobilised on polystyrene beads by flow cytometry. The inhibitor also potentiated a recently described platelet function assay based on stirring **vWf** immobilised on polystyrene beads with platelet rich plasma (PRP). Upon addition of mAb IV.3, potentiation of **vWf** bead-induced platelet activation was lost indicating that the enhancement of platelet activation was Fc receptor-dependent. Since the ELISA described can be used to quantitate **vWf** and to detect inhibitors to **vWf** in plasma samples, the method should prove useful in differentiating acquired vWd from congenital vWd.

L11 ANSWER 9 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:55489 BIOSIS

DOCUMENT NUMBER: PREV199799354692
TITLE: Von **Willebrand** factor (**VWF**) bead assay: A novel platelet hemostatic test sensitive to loss of ATP release and glycoprotein Ib in sorted platelet concentrates.
AUTHOR(S): Wang, Y.; Palmer, P.; **Stewart, M. W.**; Shaw, A. R. E.; Etches, W.; Boshkov, L. K.
CORPORATE SOURCE: Lab. Med. Pathol., Univ. Alberta Hosp., Edmonton, AB Canada
SOURCE: Blood, (1996) Vol. 88, No. 10 SUPPL. 1 PART 1-2, pp. 628A. Meeting Info.: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L11 ANSWER 10 OF 28 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 97025240 MEDLINE
DOCUMENT NUMBER: 97025240 PubMed ID: 8871463
TITLE: Bleeding in a patient taking Lorenzo's oil: evidence for a vascular defect.
AUTHOR: Chai B C; Etches W S; **Stewart M W**; Siminoski K
CORPORATE SOURCE: University of Alberta, Edmonton, Canada.
SOURCE: POSTGRADUATE MEDICAL JOURNAL, (1996 Feb) 72 (844) 113-4. Journal code: PFX; 0234135. ISSN: 0032-5473.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970227
Last Updated on STN: 19970227
Entered Medline: 19970210
AB We describe a man with adrenoleukodystrophy receiving Lorenzo's oil (glycerol trioleate and glycerol trierucate) who developed purpura, petechiae, and bleeding. Bleeding time was markedly increased (>20 min), although he had only borderline thrombocytopenia (120 x 10(9)/1) and conventional platelet aggregation studies were normal (except for a borderline response to low concentration collagen), as were results using a new technique employing immobilised von **Willebrand** factor. Together these results suggest that bleeding in this man resulted from a defect in vascular wall function or in the interaction of platelets with the endothelium.

L11 ANSWER 11 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:56006 BIOSIS
DOCUMENT NUMBER: PREV199799355209
TITLE: Detection of IgM **VWF** inhibitor associated with clinical bleeding.
AUTHOR(S): Boshkov, L. K.; Ritchie, D. B. C.; Dasgupta, M.; Etches, W.; **Stewart, M. W.**
CORPORATE SOURCE: Lab. Med. Pathol., Univ. Alberta Hosp., Edmonton, AB Canada
SOURCE: Blood, (1996) Vol. 88, No. 10 SUPPL. 1 PART 1-2, pp. 72B. Meeting Info.: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L11 ANSWER 12 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:46381 BIOSIS
DOCUMENT NUMBER: PREV199799345584
TITLE: Evaluation of stored platelets by von **Willebrand** factor (**VWF**) bead assay.
AUTHOR(S): Palmer, P.; **Stewart, M.**; Shaw, A. R. E.; Etches, W.; Boshkov, L. K.
CORPORATE SOURCE: Lab. Med. Pathol., Univ. Alberta, Edmonton, AB Canada
SOURCE: Transfusion (Bethesda), (1996) Vol. 36, No. 9 SUPPL., pp. 63S. Meeting Info.: 49th Annual Meeting of the American Association of Blood Banks Orlando, Florida, USA October 12-16, 1996
ISSN: 0041-1132.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L11 ANSWER 13 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:20202 BIOSIS
DOCUMENT NUMBER: PREV200200020202
TITLE: Method for determining platelet function.
AUTHOR(S): Shaw, A. R. E.; **Stewart, M. W.**
CORPORATE SOURCE: Edmonton Canada
ASSIGNEE: ALBERTA CANCER BOARD
PATENT INFORMATION: US 5427913 June 27, 1995
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (June 27, 1995) Vol. 1175, No. 4, pp. 2467.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English

L11 ANSWER 14 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:51142 BIOSIS
DOCUMENT NUMBER: PREV199698623277
TITLE: Uremic platelets exposed to **VWF**-coated beads show both abnormally low and high platelet activation.
AUTHOR(S): Boshkov, L. K. (1); **Stewart, M. W.**; Etches, W. S.; Shaw, A. R. E.; Ulan, R.
CORPORATE SOURCE: (1) Dep. Lab. Med., Univ. Alberta Hosp., Edmonton, AB Canada
SOURCE: Blood, (1995) Vol. 86, No. 10 SUPPL. 1, pp. 866A. Meeting Info.: 37th Annual Meeting of the American Society of Hematology Seattle, Washington, USA December 1-5, 1995
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L11 ANSWER 15 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:49894 BIOSIS
DOCUMENT NUMBER: PREV199698622029
TITLE: Platelet activation by immobilised Von **Willebrand** factor-coated beads: Evidence for a novel adhesion

mechanism involving alpha-v-beta-3, and GPIIb/IIIa.
AUTHOR(S): Shaw, A. R. E.; Etches, W. S.; Poppema, S.; Gordon, P. A.; **Stewart, M. W.**
CORPORATE SOURCE: Univ. Albert, Edmonton, AB Canada
SOURCE: Blood, (1995) Vol. 86, No. 10 SUPPL. 1, pp. 554A.
Meeting Info.: 37th Annual Meeting of the American Society of Hematology Seattle, Washington, USA December 1-5, 1995
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L11 ANSWER 16 OF 28 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:477756 CAPLUS
DOCUMENT NUMBER: 121:77756
TITLE: Methods for determining platelet function
INVENTOR(S): Shaw, Andrew R. E.; **Stewart, Michael W.**
PATENT ASSIGNEE(S): Alberta Cancer Board, Can.
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9412664	A1	19940609	WO 1993-CA521	19931203
W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5427913	A	19950627	US 1992-985679	19921203
CA 2160982	AA	19940609	CA 1993-2160982	19931203
AU 9455582	A1	19940622	AU 1994-55582	19931203
EP 672170	A1	19950920	EP 1994-900691	19931203
EP 672170	B1	19990811		
R: AT, BE, CH, DE, DK, ES, FR, GB, IE, IT, LI, NL, SE				
AT 183243	E	19990815	AT 1994-900691	19931203
US 5952184	A	19990914	US 1995-433084	19950503

PRIORITY APPLN. INFO.: US 1992-985679 19921203
WO 1993-CA521 19931203

AB The invention provides a method for detg. platelet activation in a mammal in response to von **Willebrand** factor (**vWf**) comprising providing platelets from the mammal, contacting the platelets in suspension with immobilized **vWf** or an effective fragment or analog thereof while applying to the platelets an effective mech. stimulus for an effective period of time and detg. the platelet activation produced. The invention also provides a method for detecting a bleeding disorder in a human. Further, the invention provides a method for monitoring the efficacy of pharmacol. agents affecting platelet function in vivo. Platelet rich plasma of healthy volunteers was prepd. and stirred at 500 rpm for 5 min with 4.2 .mu.m polystyrene beads directly coated with **vWf**. Platelet activation was detd. by measuring ATP release. The range of values was 146-923 pmol ATP/108 platelets; mean aggregation was 61.97. The mean aggregation value was 38.24 for 18 patients with bleeding disorders.

L11 ANSWER 17 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:57060 BIOSIS
DOCUMENT NUMBER: PREV199598071360
TITLE: Von **Willebrand** factor inhibitor associated with a mild bleeding diathesis.
AUTHOR(S): **Stewart, M. W.** (1); Etches, W. S.; Petryk, L.; McAdam, L.; Shaw, A. R. E.; Gordon, P. A.
CORPORATE SOURCE: (1) Dep. Lab. Med. and Pathol., Univ. Alberta Hosp., Edmonton, AB Canada
SOURCE: Blood, (1994) Vol. 84, No. 10 SUPPL. 1, pp. 682A.
Meeting Info.: Abstracts Submitted to the 36th Annual Meeting of the American Society of Hematology Nashville, Tennessee, USA December 2-6, 1994
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L11 ANSWER 18 OF 28 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 92188334 MEDLINE
DOCUMENT NUMBER: 92188334 PubMed ID: 1798965
TITLE: Effect of chlorobutanol and DDAVP on whole blood aggregation/clotting.
COMMENT: Erratum in: Thromb Res 1992 Mar 1;65(4-5):669
AUTHOR: **Stewart M W**; Gordon P A
CORPORATE SOURCE: Department of Laboratory Medicine, University of Alberta Hospitals, Edmonton, Canada.
SOURCE: THROMBOSIS RESEARCH, (1991 Dec 15) 64 (6) 757-62.
Journal code: VRN; 0326377. ISSN: 0049-3848.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920424
Last Updated on STN: 19920424
Entered Medline: 19920415

L11 ANSWER 19 OF 28 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 90223370 MEDLINE
DOCUMENT NUMBER: 90223370 PubMed ID: 2326779
TITLE: Rapid diagnosis of von **Willebrand**'s disease using ELISA technology.
AUTHOR: Gilchrist M; **Stewart M W**; Etches W S; Gordon P A
CORPORATE SOURCE: Department of Laboratory Medicine, University of Alberta Hospitals, Edmonton, Canada.
SOURCE: THROMBOSIS RESEARCH, (1990 Feb 15) 57 (4) 659-64.
Journal code: VRN; 0326377. ISSN: 0049-3848.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199005
ENTRY DATE: Entered STN: 19900622
Last Updated on STN: 19990129

Entered Medline: 19900524

L11 ANSWER 20 OF 28 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 88278274 MEDLINE
DOCUMENT NUMBER: 88278274 PubMed ID: 2839913
TITLE: Analysis of vWf binding to platelets by flow cytometry.
AUTHOR: **Stewart M W**; Etches W S; Gordon P A
CORPORATE SOURCE: Department of Laboratory Medicine, University of Alberta Hospitals, Edmonton, Canada.
SOURCE: THROMBOSIS RESEARCH, (1988 May 1) 50 (3) 455-60.
Journal code: VRN; 0326377. ISSN: 0049-3848.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198808
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19990129
Entered Medline: 19880824

L11 ANSWER 21 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1989:67999 BIOSIS
DOCUMENT NUMBER: BR36:34790
TITLE: PIGS WITH SEVERE VON **WILLEBRAND**'S DISEASE ARE RESISTANT TO EXPERIMENTAL INFECTIVE ENDOCARDITIS.
AUTHOR(S): JOHNSON C M; **STEWART M**; ZOECKLEIN L J; BOWIE E J W
CORPORATE SOURCE: MAYO CLIN. AND MAYO FOUND., ROCHESTER, MN.
SOURCE: 61ST SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION, WASHINGTON, D.C., USA, NOVEMBER 14-17, 1988. CIRCULATION, (1988) 78 (4 PART 2), II134.
CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L11 ANSWER 22 OF 28 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 87195897 MEDLINE
DOCUMENT NUMBER: 87195897 PubMed ID: 3571753
TITLE: Treatment of severe platelet dysfunction and hemorrhage after cardiopulmonary bypass: reduction in blood product usage with desmopressin.
AUTHOR: Czer L S; Bateman T M; Gray R J; Raymond M; **Stewart M E**; Lee S; Goldfinger D; Chaux A; Matloff J M
SOURCE: JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, (1987 May) 9 (5) 1139-47.
Journal code: H50; 8301365. ISSN: 0735-1097.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198706
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19970203
Entered Medline: 19870602
AB Impairment of platelet function commonly occurs after cardiopulmonary bypass, and may result in substantial bleeding. Because desmopressin acetate (a synthetic analogue of vasopressin) shortens bleeding time in a variety of platelet disorders, a controlled clinical trial of intravenous desmopressin was performed in 39 patients with excessive mediastinal bleeding (greater than 100 ml/h) and a prolonged template bleeding time (greater than 10 minutes) more than 2 hours after termination of cardiopulmonary bypass. Twenty-three desmopressin recipients and 16 control patients (no desmopressin) were similar in surgical procedure, pump time, platelet count, template bleeding time and amount of bleeding before therapy (p = NS). Compared with the control group, the patients receiving desmopressin (20 micrograms; mean 0.3 micrograms/kg) utilized fewer blood products (29 +/- 19 versus 15 +/- 13 units/patient; p less than 0.05), especially platelets (12 +/- 9 versus 4 +/- 7 units/patient; p = 0.004), while achieving a similarly effective reduction in mediastinal bleeding (4.8- and 4.3-fold, p = 0.001 for both). Severe platelet dysfunction was partially corrected within 1 hour after desmopressin infusion, during which interval no blood products were administered: the template bleeding time shortened (from 17 to 12.5 minutes, p less than 0.05), whereas the platelet count remained unchanged (at 96 +/- 35 and 105 +/- 31 X 10(3)/mm3, p = NS). The plasma levels of two factor VIII components increased: procoagulant activity (VIII:C) from 0.97 +/- 0.43 to 1.52 +/- 0.74 units/ml (p less than 0.05) and von **Willebrand** factor (VIII:**vWF**) from 1.28 to 1.78 units/ml (p less than 0.05); these increases correlated with the shortening of the bleeding time (p less than 0.01).(ABSTRACT TRUNCATED AT 250 WORDS)

L11 ANSWER 23 OF 28 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 86279518 MEDLINE
DOCUMENT NUMBER: 86279518 PubMed ID: 3488343
TITLE: Inheritance of a new bleeding disease in a herd of swine with **Willebrand**'s disease.
AUTHOR: Thiele G L; Rempel W E; Fass D N; Bowie E J; **Stewart M**; Zoecklein L
CONTRACT NUMBER: HL-17430 (NHLBI)
SOURCE: JOURNAL OF HEREDITY, (1986 May-Jun) 77 (3) 179-82.
Journal code: IC7; 0375373. ISSN: 0022-1503.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198609
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19990129
Entered Medline: 19860916
AB A herd of swine affected by **Willebrand**'s disease was begun in 1967 at the Mayo Clinic in order to study the inherited hemostatic abnormality in swine as a model for the human disease. Affected individuals have bleeding times in excess of 15 minutes, extremely low levels of **Willebrand** factor (less than or equal to 0.25 percent of normal), and decreased levels of VIII coagulant activity. Individuals with long bleeding times, higher levels of **Willebrand** factor and normal levels of VIII coagulant activity began to appear in the colony. It is hypothesized that this new (N) condition is inherited as a simple

autosomal recessive (N/n) at a locus separate and independent of the similarly autosomal recessive (A/a) von **Willebrand** locus. In addition, the **Willebrand** locus is epistatic to the N locus, i.e., individuals will only express the new condition provided there is at least one normal allele at the von **Willebrand** locus. Therefore, individuals with genotype aa--are all von **Willebrand** phenotypically, and A-nn individuals have the new disease.

L11 ANSWER 24 OF 28 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 86272556 MEDLINE
DOCUMENT NUMBER: 86272556 PubMed ID: 3488141
TITLE: A competitive ELISA technique for the measurement of von **Willebrand** factor antigen (**vWF**:Ag) using staphylococcal protein A peroxidase.
AUTHOR: Brien W F; **Stewart M W**
SOURCE: CLINICAL BIOCHEMISTRY, (1986 Jun) 19 (3) 179-82.
Journal code: DBV; 0133660. ISSN: 0009-9120.
PUB. COUNTRY: Canada
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198609
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860917
AB A competitive ELISA technique for measurement of von **Willebrand** factor antigen (**vWF**:Ag) using Staphylococcal Protein A peroxidase is described. The standard used in this assay is partially purified Factor VIII:C/**vWF** which has been standardized against a conventional method (electroimmunoassay). The results show a close correlation (correlation coefficient 0.956) as compared to the standard Laurell electroimmunoassay technique. Inter-assay and intra-assay coefficients of variation were less than 5%. The technique is simple to perform and results may be obtained within three hours of specimen collection.

L11 ANSWER 25 OF 28 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 86251308 MEDLINE
DOCUMENT NUMBER: 86251308 PubMed ID: 3088043
TITLE: Transplantation of normal bone marrow into a pig with severe von **Willebrand**'s disease.
AUTHOR: Bowie E J; Solberg L A Jr; Fass D N; Johnson C M; Knutson G J; **Stewart M L**; Zoecklein L J
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1986 Jul) 78 (1) 26-30.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198608
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19990129
Entered Medline: 19860806
AB Bone marrow from a normal male pig was transplanted into a related female pig with severe homozygous von **Willebrand**'s disease (vWd). After engraftment the circulating leukocytes were of the male karyotype, and the platelets were strongly positive for von **Willebrand** factor (**vWF**) by indirect immunofluorescence. The average level of **vWF** was 1.96 U/dl and of ristocetin cofactor was 2.8 U/dl. The ear immersion bleeding time before transplantation was consistently more than 15 min and afterwards varied between 5 min and more than 15 min. Transfused **vWF** corrected the bleeding time at a level of 10 U/dl, which is lower than that required for a von **Willebrand** pig. We concluded that: the plasmatic compartment is only minimally replenished by the **vWF** from platelets and megakaryocytes; and the platelet **vWF** alone only partially corrects the abnormal tests of the hemostatic mechanism in severe vWd.

L11 ANSWER 26 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1986:27359 BIOSIS
DOCUMENT NUMBER: BR30:27359
TITLE: TRANSPLANTATION OF NORMAL MARROW INTO A PIG WITH VON **WILLEBRAND**'S DISEASE.
AUTHOR(S): BOWIE E J W; SOLBERG L A; FASS D N; KNUTSON G J; **STEWART M L**; ZOECKLEIN L; EVANS R G
CORPORATE SOURCE: HEMATOLOGY RESEARCH, MAYO CLINIC AND FOUNDATION, ROCHESTER, MN.
SOURCE: 58TH ANNUAL MEETING OF THE CENTRAL SOCIETY FOR CLINICAL RESEARCH , CHICAGO, ILL., USA, NOV. 6-8. 1985. CLIN RES, (1985) 33 (4), 879A.
CODEN: CLREAS. ISSN: 0009-9279.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L11 ANSWER 27 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1983:106635 BIOSIS
DOCUMENT NUMBER: BR25:31635
TITLE: SPONTANEOUS PLATELET AGGREGATION ACTIVITY PRODUCED BY **WILLEBRAND** FACTOR MODIFIED BY MONO CLONAL ANTIBODIES.
AUTHOR(S): HEILER G; FASS D N; KATZMANN J A; **STEWART M**; BOWIE E J W
CORPORATE SOURCE: SECT. HEMOTOL. RES., MAYO CLIN. AND FOUND., ROCHESTER, MINN. 55901.
SOURCE: 55TH SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION, DALLAS, TEX., USA, NOV. 15-18, 1982. AM HEART ASSOC MONOGR, (1982) 0 (91), II-298.
CODEN: AHMOAH. ISSN: 0065-8499.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L11 ANSWER 28 OF 28 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 79198003 MEDLINE
DOCUMENT NUMBER: 79198003 PubMed ID: 312982
TITLE: Hypofibrinogenemia-dysfibrinogenemia and von **Willebrand**'s disease in the same family.
AUTHOR: Owen C A Jr; Bowie E J; Fass D N; Perez R A; Cole T L; **Stewart M**
SOURCE: MAYO CLINIC PROCEEDINGS, (1979 Jun) 54 (6) 375-80.
Journal code: LLY; 0405543. ISSN: 0025-6196.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 197909
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19990129
Entered Medline: 19790901
AB Two Puerto Rican families were studied. One family included a number of members with dysfibrinogenemia occasionally associated with hypofibrinogenemia. The second family had members with von **Willebrand**'s disease. The two diseases merged in the proband's immediate family; the affected members of this family exhibited a mild bleeding disorder. Others in the two families had no obvious bleeding tendency.

=> dis his

(FILE 'HOME' ENTERED AT 10:43:02 ON 13 MAY 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 10:43:14 ON 13 MAY 2002
L1 704921 S THROMB?
L2 12366 S L1 AND WILLEBRAND
L3 0 S L2 AND BIFINCTION?
L4 8 S L2 AND BIFUNCTION?
L5 5 DUP REM L4 (3 DUPLICATES REMOVED)
L6 49 S L2 AND VEGF?
L7 24 DUP REM L6 (25 DUPLICATES REMOVED)
L8 0 S L7 AND ADMINIST?
L9 6154 S STEWART M?/AU OR PERSON R?/AU OR NOUJAIM A?/AU
L10 60 S L9 AND (VWF OR WILLEBRAND?)
L11 28 DUP REM L10 (32 DUPLICATES REMOVED)

=> s l1 and (cancer? or neoplast? or angio? tumor? or tumour?)
L12 38450 L1 AND (CANCER? OR NEOPLAST? OR ANGIO? TUMOR? OR TUMOUR?)

=> s l12 and (vwf or willebrand)
L13 258 L12 AND (VWF OR WILLEBRAND)

=> s l13 and VEGF?
L14 14 L13 AND VEGF?

=> dup rem l14 ibib abs
PROCESSING COMPLETED FOR L14
L15 6 DUP REM L14 IBIB ABS (8 DUPLICATES REMOVED)

=> dis l15 1-6 ibib abs kwic

L15 ANSWER 1 OF 6 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002182450 IN-PROCESS
DOCUMENT NUMBER: 21913062 PubMed ID: 11916242
TITLE: Aerosol delivery of PEI-p53 complexes inhibits B16-F10 lung metastases through regulation of angiogenesis.
AUTHOR: Gautam Ajay; Densmore Charles L; Melton Sara; Golunski Eva; Waldrep J Clifford
CORPORATE SOURCE: Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, Texas 77030, USA.
SOURCE: CANCER GENE THERAPY, (2002 Jan) 9 (1) 28-36.
Journal code: 9432230. ISSN: 0929-1903.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020403
Last Updated on STN: 20020403
AB Inhibition of pulmonary metastases poses a difficult clinical challenge for current therapeutic regimens. We have developed an aerosol system utilizing a cationic polymer, polyethyleneimine (PEI), for topical gene delivery to the lungs as a novel approach for treatment of lung **cancer**. Using a B16-F10 murine melanoma model in C57BL/6 mice, we previously demonstrated that aerosol delivery of PEI-p53 DNA resulted in highly significant reductions in the tumor burden (P < .001) in treated animals, and also lead to about 50% increase in the mean length of survival of the mice-bearing B16-F10 lung tumors. The mechanisms of this antitumor effect of p53 are investigated in this report. Here, we demonstrate that the p53 transfection leads to an up-regulation of the antiangiogenic factor **thrombospondin**-1 (TSP-1) in the lung tissue and the serum of the mice. Furthermore, there is a down-regulation of vascular endothelial growth factor (**VEGF**) in the lung tissue and serum of the B16-F10 tumor-bearing mice treated with PEI-p53 DNA complexes, compared with untreated tumor-bearing animals. In addition, staining for von **Willebrand** factor (**vWF**), a marker for the angiogenic blood vessels, revealed that p53 treatment leads to a decrease in the angiogenic phenotype of the B16-F10 tumors. Immunohistochemistry for transgene expression reveals that the PEI-p53 aerosol complexes transfect mainly the epithelial cells lining the airways, with diffuse transfection in the alveolar lining cells, as well as, the tumor foci in the lung tissue. There was also some evidence of apoptosis in the lung tumor foci of animals treated with p53. The data suggest that aerosol delivery of PEI-p53 complexes leads to inhibition of B16-F10 lung metastases, in part by suppression of angiogenesis.
AB . . . a cationic polymer, polyethyleneimine (PEI), for topical gene delivery to the lungs as a novel approach for treatment of lung **cancer**. Using a B16-F10 murine melanoma model in C57BL/6 mice, we previously demonstrated that aerosol delivery of PEI-p53 DNA resulted in. . . are investigated in this report. Here, we demonstrate that the p53 transfection leads to an up-regulation of the antiangiogenic factor **thrombospondin**-1 (TSP-1) in the lung tissue and the serum of the mice. Furthermore, there is a down-regulation of vascular endothelial growth factor (**VEGF**) in the lung tissue and serum of the B16-F10 tumor-bearing mice treated with PEI-p53 DNA complexes, compared with untreated tumor-bearing animals. In addition, staining for von **Willebrand** factor (**vWF**), a marker for the angiogenic blood vessels, revealed that p53 treatment leads to a decrease in the angiogenic phenotype of. . .

L15 ANSWER 2 OF 6 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001642260 MEDLINE
DOCUMENT NUMBER: 21553580 PubMed ID: 11696172
TITLE: Angiogenesis and phenotypic alteration of alveolar capillary endothelium in areas of **neoplastic** cell

spread in primary lung adenocarcinoma.
AUTHOR: Jin E; Ghazizadeh M; Fujiwara M; Nagashima M; Shimizu H; Ohaki Y; Arai S; Gomibuchi M; Takemura T; Kawanami O
CORPORATE SOURCE: Department of Molecular Pathology, Institute of Gerontology, Nippon Medical School, Kawasaki, Japan.
SOURCE: PATHOLOGY INTERNATIONAL, (2001 Sep) 51 (9) 691-700. Journal code: 9431380. ISSN: 1320-5463.
PUB. COUNTRY: Australia
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011107
Last Updated on STN: 20020123
Entered Medline: 20011214

AB Normal alveolar capillary endothelium is quiescent in nature and displays anticoagulant **thrombomodulin** (TM) on its surface. The cytoplasms of these endothelial cells are ultrastructurally non-fenestrated type, and they barely express von **Willebrand** factor (**vWf**).
Alveolar fibrosis is accompanied by a capillary endothelium reactive for **vWf**, and a loss of TM expression. In primary lung adenocarcinoma, neovascularization occurs in association with alveolar fibrosis. In order to study basic factors related to angiogenesis and phenotypic changes of the capillaries located in tumor-bearing alveolar walls, we examined 37 primary lung adenocarcinomas with electron microscopy and confocal laser scanning microscopy with antibodies for TM, **vWf**, vascular endothelial growth factor (**VEGF**), and its receptors (KDR and Flt-1), and proliferating markers (Ki-67/proliferating cell nuclear antigen). Tissues microdissected specifically from alveolar walls were used for reverse transcription-polymerase chain reaction (RT-PCR) to assess expressions of mRNA isoforms of **VEGF** and its receptors.
New capillary branching was found by ultrastructural study in the alveolar walls in 12% of the patients. Nuclei of the capillary endothelial cells were reactive for proliferating cell markers. Endothelial fenestrae were developed in 65% of the patients, TM reactivity was lost in the alveolar capillaries, and their cell cytoplasms obtained a reactivity for **vWf** through a transitional mosaic-like distribution pattern of both antigens. Besides cytoplasmic **VEGF** expression in **neoplastic** cells, tumor-bearing alveolar walls showed significant expression of mRNA of **VEGF165** and KDR. These findings imply that angiogenesis and phenotypic changes of the alveolar capillaries are closely related to a higher expression of tumor-associated **VEGF165** and of KDR in the alveolar walls in primary lung adenocarcinoma.
TI Angiogenesis and phenotypic alteration of alveolar capillary endothelium in areas of **neoplastic** cell spread in primary lung adenocarcinoma.
AB Normal alveolar capillary endothelium is quiescent in nature and displays anticoagulant **thrombomodulin** (TM) on its surface. The cytoplasms of these endothelial cells are ultrastructurally non-fenestrated type, and they barely express von **Willebrand** factor (**vWf**).
Alveolar fibrosis is accompanied by a capillary endothelium reactive for **vWf**, and a loss of TM expression. In primary lung adenocarcinoma, neovascularization occurs in association with alveolar fibrosis. In order to. . . alveolar walls, we examined 37 primary lung adenocarcinomas with electron microscopy and confocal laser scanning microscopy with antibodies for TM, **vWf**, vascular endothelial growth factor (**VEGF**), and its receptors (KDR and Flt-1), and proliferating markers (Ki-67/proliferating cell nuclear antigen). Tissues microdissected specifically from alveolar walls were used for reverse transcription-polymerase chain reaction (RT-PCR) to assess expressions of mRNA isoforms of **VEGF** and its receptors. New capillary branching was found by ultrastructural study in the alveolar walls in 12% of the patients.. . . 65% of the patients, TM reactivity was lost in the alveolar capillaries, and their cell cytoplasms obtained a reactivity for **vWf** through a transitional mosaic-like distribution pattern of both antigens. Besides cytoplasmic **VEGF** expression in **neoplastic** cells, tumor-bearing alveolar walls showed significant expression of mRNA of **VEGF165** and KDR. These findings imply that angiogenesis and phenotypic changes of the alveolar capillaries are closely related to a higher expression of tumor-associated **VEGF165** and of KDR in the alveolar walls in primary lung adenocarcinoma.
CT . . .
Receptor Protein-Tyrosine Kinases: GE, genetics
Receptors, Growth Factor: AN, analysis
Receptors, Growth Factor: GE, genetics
Reverse Transcriptase Polymerase Chain Reaction
Thrombomodulin: AN, analysis
von Willebrand Factor: AN, analysis
CN. . . Growth Factors); 0 (Ki-67 Antigen); 0 (Lymphokines); 0 (Proliferating Cell Nuclear Antigen); 0 (RNA, Messenger); 0 (Receptors, Growth Factor); 0 (**Thrombomodulin**); 0 (vascular endothelial cell growth factor receptor); 0 (vascular permeability factor); 0 (von **Willebrand** Factor); EC 2.7.11.- (Receptor Protein-Tyrosine Kinases)

L15 ANSWER 3 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:100666 BIOSIS
DOCUMENT NUMBER: PREV200100100666
TITLE: **Neoplastic** invasion of primary adeno-carcinoma induces phenotypic alteration to alveolar capillary endothelium in the lung.
AUTHOR(S): Kawanami, O. (1); Jin, E. (1); Ghazizadeh, M. (1); Fujiwara, M. (1); Jiang, L. (1); Shimizu, H. (1); Arai, S. (1); Ohaki, Y. (1)
CORPORATE SOURCE: (1) Department of Molecular Pathology, Institute of Gerontology and Hokusoh Hospital, Nippon Medical School, Kawasaki Japan
SOURCE: Journal of Submicroscopic Cytology and Pathology, (July, 2000) Vol. 32, No. 3, pp. 363. print.
Meeting Info.: XIth International Vascular Biology Meeting Geneva, Switzerland September 05-09, 2000
ISSN: 1122-9497.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
TI **Neoplastic** invasion of primary adeno-carcinoma induces phenotypic alteration to alveolar capillary endothelium in the lung.
IT . . .
(Respiration); Tumor Biology
IT Parts, Structures, & Systems of Organisms
alveolar capillary endothelium: circulatory system, respiratory system; lung: respiratory system; **neoplastic** cell; tumor cell

IT Diseases
primary adenocarcinoma: **neoplastic disease**
IT Chemicals & Biochemicals
VEGF [vascular endothelial growth factor]; mRNA [messenger RNA]; **thrombomodulin**: expression; von **Willebrand** factor [**vWf**]: expression

L15 ANSWER 4 OF 6 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999342075 MEDLINE
DOCUMENT NUMBER: 99342075 PubMed ID: 10411932
TITLE: Regulation of vascular endothelial growth factor production and angiogenesis by the cytoplasmic tail of tissue factor.
AUTHOR: Abe K; Shoji M; Chen J; Bierhaus A; Danave I; Micko C; Casper K; Dillehay D L; Nawroth P P; Rickles F R
CORPORATE SOURCE: Emory University School of Medicine, Atlanta, GA 30333, USA.
CONTRACT NUMBER: CA22202 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Jul 20) 96 (15) 8663-8. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990910
Last Updated on STN: 19990910
Entered Medline: 19990823

AB Tissue factor (TF), a transmembrane receptor for coagulation factor VII/VIIa, is aberrantly expressed in human **cancers**. We demonstrated a significant correlation between TF and vascular endothelial growth factor (**VEGF**) production in 13 human malignant melanoma cell lines ($r(2) = 0.869$, $P < 0.0001$). Two of these cell lines, RPMI-7951, a high TF and **VEGF** producer, and WM-115, a low TF and **VEGF** producer, were grown s.c. in severe combined immunodeficient mice. The high-producer cell line generated solid tumors characterized by intense vascularity, whereas the low producer generated relatively avascular tumors, as determined by immunohistologic staining of tumor vascular endothelial cells with anti-von **Willebrand** factor antibody. To investigate the structure-function relationship of TF and **VEGF**, a low-producer melanoma cell line (HT144) was transfected with a TF cDNA containing the full-length sequence, a cytoplasmic deletion mutant lacking the coding sequence for the distal three serine residues (potential substrates for protein kinase C), or an extracellular domain mutant, which has markedly diminished function for activation of factor X. Cells transfected with the full-length sequence produced increased levels of both TF and **VEGF**. Transfectants with the full-length sequence and the extracellular domain mutant produced approximately equal levels of **VEGF** mRNA. However, cells transfected with the cytoplasmic deletion mutant construct produced increased levels of TF, but little or no **VEGF**. Thus, the cytoplasmic tail of TF plays a role in the regulation of **VEGF** expression in some tumor cells.
AB Tissue factor (TF), a transmembrane receptor for coagulation factor VII/VIIa, is aberrantly expressed in human **cancers**. We demonstrated a significant correlation between TF and vascular endothelial growth factor (**VEGF**) production in 13 human malignant melanoma cell lines ($r(2) = 0.869$, $P < 0.0001$). Two of these cell lines, RPMI-7951, a high TF and **VEGF** producer, and WM-115, a low TF and **VEGF** producer, were grown s.c. in severe combined immunodeficient mice. The high-producer cell line generated solid tumors characterized by intense vascularity, . . . whereas the low producer generated relatively avascular tumors, as determined by immunohistologic staining of tumor vascular endothelial cells with anti-von **Willebrand** factor antibody. To investigate the structure-function relationship of TF and **VEGF**, a low-producer melanoma cell line (HT144) was transfected with a TF cDNA containing the full-length sequence, a cytoplasmic deletion mutant. . . . diminished function for activation of factor X. Cells transfected with the full-length sequence produced increased levels of both TF and **VEGF**. Transfectants with the full-length sequence and the extracellular domain mutant produced approximately equal levels of **VEGF** mRNA. However, cells transfected with the cytoplasmic deletion mutant construct produced increased levels of TF, but little or no **VEGF**. Thus, the cytoplasmic tail of TF plays a role in the regulation of **VEGF** expression in some tumor cells.

CT . . . Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Endothelial Growth Factors: GE, genetics
*Endothelial Growth Factors: ME, metabolism
Endothelium, Vascular: CY, cytology
Gene Expression Regulation, Neoplastic
Immunohistochemistry
Lymphokines: GE, genetics
*Lymphokines: ME, metabolism
*Melanoma: GE, genetics
Mice
Mice, SCID
Neoplasm Transplantation
*Neovascularization, Pathologic: GE, genetics
RNA, Messenger: ME, metabolism
Sequence Deletion
Thromboplastin: GE, genetics
***Thromboplastin: ME, metabolism**
Transfection
Tumor Cells, Cultured
von Willebrand Factor: IM, immunology
RN **9035-58-9 (Thromboplastin)**
CN 0 (Endothelial Growth Factors); 0 (Lymphokines); 0 (RNA, Messenger); 0 (vascular permeability factor); 0 (von **Willebrand** Factor)

L15 ANSWER 5 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:95753 BIOSIS
DOCUMENT NUMBER: PREV199800095753
TITLE: Why do immature hemangiomas regress.
AUTHOR(S): Eeckhout, I. (1); Leaute-Labreze, C.; Taieb, A.
CORPORATE SOURCE: (1) Serv. Dermatol., Hop. Univ., De Pintelaan 185, B-9000 Gent Belgium
SOURCE: Annales de Dermatologie et de Venereologie, (Nov., 1997) Vol. 124, No. 11, pp. 800-804. ISSN: 0151-9638.
DOCUMENT TYPE: Article
LANGUAGE: French
IT . . .
Systems of Organisms

endothelial cells; fibroblasts; keratinocytes: integumentary system; mast cells: immune system; melanocytes: integumentary system

IT Diseases
hemangioma: regression, **neoplastic** disease, immature

IT Chemicals & Biochemicals
acidic fibroblast growth factor [aFGF]; alpha smooth muscle cell actin; angiogenesis inhibiting factors; angiogenesis. . . interferon-alpha: antineoplastic - drug, 2b, 2a; interleukin 12; platelet factor 4; platelet-derived growth factor; proliferating cell nuclear antigen; syndecans; thalidomide; **thrombospondin**; tissue inhibitors of metalloproteinases [TIMP]; vascular endothelial growth factor [**VEGF**]; vascular permeability factor [VPF]; von **Willebrand** factor; CD31

RN 50-35-1 (THALIDOMIDE)
9050-30-0 (HEPARAN SULFATE)
153-87-7QD (INTEGRINS)
60791-49-3QD (INTEGRINS)
81669-70-7D (METALLOPROTEINASES)
109319-16-6 (VON **WILLEBRAND** FACTOR)
132579-20-5 (ACTIN)

L15 ANSWER 6 OF 6 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 94297320 MEDLINE
DOCUMENT NUMBER: 94297320 PubMed ID: 7517738
TITLE: **Tumour** angiogenesis.
AUTHOR: Le Querrec A; Duval D; Tobelem G
CORPORATE SOURCE: Laboratoire d'Hematologie, CHU, Caen, France.
SOURCE: BAILLIERES CLINICAL HAEMATOLOGY, (1993 Sep) 6 (3) 711-30.
Ref: 92
Journal code: BCH; 8800474. ISSN: 0950-3536.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940818
Last Updated on STN: 19960129
Entered Medline: 19940808

AB The progressive emergence of a close relationship between the formation of blood vessels in the vicinity of **tumour** cells and the development and spreading of **tumours**, strongly suggests that angiogenesis might be a prerequisite for **tumour** development. Angiogenesis starts and develops in response to two sets of extracellular signals: soluble angiogenic factors and extracellular matrix. Different experimental models have been used to study angiogenesis in vivo, but they have numerous limitations. Three-dimensional culture systems reconstitute normal interactions between endothelial cells and the surrounding extracellular matrix. Numerous parameters including angiogenic growth factors and cytokines, cell-to-cell interactions and cell-to-extracellular matrix adhesion influence the growth and differentiation of endothelial cells in vitro as well as in vivo. Angiogenesis plays a major role not only in **tumour** growth but also in metastasis development. Mechanisms of switching to angiogenic phenotype have been recently described and onset of angiogenic activity is now recognized as another discrete step in tumorigenesis. **Tumour** cells can induce b-FGF expression and exportation, **VEGF** and **VEGF** receptor expression and inactivation of the **cancer** suppressor gene encoding for a fragment of **thrombospondin**. A controlled net proteolytic balance produced by **tumour** cells or endothelial cells is required to favour migration and invasion of endothelial cells and angiogenesis. The hypothesis that assessment of **tumour** angiogenesis might predict **tumour** aggressiveness in human **cancer** has recently gained support from several clinical studies. This has been shown for cutaneous melanoma, breast carcinoma, and non-small-cell lung **cancer** by quantitation of microvessels in human biopsies using von **Willebrand** factor or CD3 antigen labelling with specific antibodies. However, more specific and sensitive markers are needed to improve this approach for predicting **tumour** aggressiveness. Folkman proposed twenty years ago that inhibition of angiogenesis might represent a suitable complementary strategy for the treatment of various forms of **cancer**. Since then numerous angiostatic compounds have been identified but very few of them fit the required criteria of a potential drug. Fumagillin and particularly its synthetic analogue AGM 1470 might be developed for use in humans in the near future.

TI **Tumour** angiogenesis.

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=> dis his

(FILE 'HOME' ENTERED AT 10:43:02 ON 13 MAY 2002)

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     FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 10:43:14 ON 13 MAY 2002
L1        704921 S THROMB?
L2         12366 S L1 AND WILLEBRAND
L3             0 S L2 AND BIFINCTION?
L4             8 S L2 AND BIFUNCTION?
L5             5 DUP REM L4 (3 DUPLICATES REMOVED)
L6            49 S L2 AND VEGF?
L7            24 DUP REM L6 (25 DUPLICATES REMOVED)
L8             0 S L7 AND ADMINIST?
L9          6154 S STEWART M?/AU OR PERSON R?/AU OR NOUJAIM A?/AU
L10           60 S L9 AND (VWF OR WILLEBRAND?)
L11           28 DUP REM L10 (32 DUPLICATES REMOVED)
L12        38450 S L1 AND (CANCER? OR NEOPLAST? OR ANGIO? TUMOR? OR TUMOUR?)
L13          258 S L12 AND (VWF OR WILLEBRAND)
L14           14 S L13 AND VEGF?
L15            6 DUP REM L14 IBIB ABS (8 DUPLICATES REMOVED)

=> end
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:n

=> end
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
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CA SUBSCRIBER PRICE                                    -6.20      -6.20

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